# A RETROSPECTIVE CASE-CONTROL STUDY ON THE PRESCRIBING PRACTICES OF ANTIDEPRESSANTS ADMINISTERED TO CANCER PATIENTS AND NON-CANCER PATIENTS IN AUSTRALIA

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B. Pharm (Hons), M. Pharm (USTC)

Submitted in fulfilment of the requirements for the degree of
Master of Applied Science (Research)

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2016

# Keywords

Antidepressants, Cancer, Prescription, Psychotropic

# Abstract

*Objective:* Many cancer patients suffer from depression after diagnosis of cancer and depression continues during cancer treatment and post-treatment procedure. Continuation of untreated depression may increase hospitalisations, nonadherence to treatment and decreased survival time of cancer patients. Antidepressants are commonly used for the pharmacological treatment of depression. Concerns have been raised about the possibility of inadequate prescribing of these drugs and the risk of drug-drug interactions when prescribed to cancer patients by doctors other than psychiatrists. This study had two main aims: 1) to systematically review and meta-analyse the prevalence of antidepressant prescriptions to cancer patients as reported in the literature and to explore whether there are differences by study or patient characteristics; 2) to use a retrospective case-control study design to describe the antidepressant prescribing practices for cancer and non-cancer hospital inpatients at an Australian tertiary hospital.

*Methods:* AIM 1: The systematic literature search was undertaken according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods. The keywords, 'antidepressants', 'prescription', 'psychotropic' and 'cancer' were used in the databases including PubMed, Embase, Web of Science, Scopus and psychINFO. Pooled estimate of the prevalence of antidepressants to cancer patients (95% Confidence Interval) reported in the studies were determined by using Comprehensive meta-analysis software (Version 3 by Borenstein, Biostat, Englewood, New Jersey, US, 2015). Type, dose and follow-up of antidepressants, cancer patient characteristics and their setting, place and duration of study and prescriber details were extracted for the review from each study. Quality (low quality to high quality ranged from 1-4) and risk of bias (no risk to high bias risk ranged from 0-4) were assessed to rate the quality of the articles included in the meta-analyses. This review identified the lack of research and knowledge gaps in Australia.

AIM 2: To address these gaps, a retrospective case-control study was undertaken in a tertiary hospital. Inpatients diagnosed with cancer within the past 12 months and prescribed antidepressants were considered as 'cases'. Age and gender matched inpatients without cancer history prescribed antidepressants were included as 'controls'. Patient medication charts, clinical and socio-demographic records were abstracted from the hospital database system. Conditional logistic regression was used to compare cases and controls according to

their socio-demographic characteristics, clinical status and their antidepressant treatment profile by presenting odds ratios, 95% confidence intervals and *p* values (<0.05).

*Results:* Study 1: The search conducted for the review and meta-analysis discovered 1537 articles published between 1979 and February 2015 of which 38 met the inclusion criteria. These articles were reviewed in full for data extraction and meta-analyses. Across all studies, the pooled prevalence rate of prescribing antidepressants to cancer patients was 15.6% (95% CI= 13.3-18.3). Prescriptions were significantly less common reported in studies from Asia (7.4%; 95% CI= 4.3-12.5). Antidepressant prescriptions were more common in female (22.6%; 95% CI= 16.0-31.0) or breast cancer patients (22.6%; 95% CI= 16.0-30.9). Selective serotonin reuptake inhibitors (SSRIs) were the most frequently prescribed antidepressants. General practitioners and psychiatrists, followed by oncologists, were identified as the major providers of antidepressant prescriptions to cancer patients. Only very few studies reported the exact dose (n= 3), or the length of time (n= 3) drugs were prescribed for or detailed the follow-up regimens after the antidepressants were prescribed. Only one study was conducted in Australia and further research to determine the prescription characteristics of antidepressants to cancer patients is needed.

Study 2: Data from 75 cancer and 75 non-cancer inpatients were extracted between January 2014 and July 2015. Antidepressants were prescribed for the treatment of depression (n= 50 vs n= 59) or other mental health problem including anxiety (n= 8 vs n= 11) to cancer and non-cancer patients, respectively. The remaining cancer and non-cancer patients (n= 17 vs n= 5) were prescribed antidepressants for unidentified reasons. Mirtazapine (n= 11) was the antidepressant most commonly prescribed for the treatment of depression to cancer inpatients followed by duloxetine (n= 9) and escitalopram (n= 8). Desvenlafaxine (n= 15) was the most commonly prescribed to non-cancer inpatients, followed by mirtazapine (n= 11). Cancer patients were more commonly prescribed the recommended daily dose of antidepressants (40.68%, n= 24/59 cancer patients; 38.67%, n= 29/75 non-cancer patients). Significant differences in several sociodemographic and clinical variables were documented between cases and controls. Four cancer patients and three non-cancer patients had documented adverse side-effects from antidepressants. About one-third of cancer patients (n= 23) and more than one-fourth non-cancer patients (n= 18) had been prescribed simultaneously medicines with potential drug-drug interaction with their prescribed antidepressant. From data that could be extracted from this hospital's pharmacy database and clinical records there

appeared to be a lack of formal prescribing follow-up regimens or the clinical expertise of the prescriber of antidepressants.

*Conclusions:* There is considerable variation in the prescribing patterns of antidepressants across the world, with few studies reporting robust data on exact dose or follow-up regimens. The retrospective case-control study showed that besides depression antidepressants are commonly prescribed for other mental problems including anxiety or unidentified reason to both cancer and non-cancer patients. A number of the aspects that are limitations of the present study such as antidepressant dosing variations, incomplete follow-up and prescriber information are important aspects of prescribing requiring further study. Prospective studies that describe antidepressants prescribing to cancer patients, monitor details of reasons for prescribing, the expertise of the health care providers involved, and the follow-up arrangements are needed to ascertain whether patients are being treated according to best guidelines available for the prescribing of antidepressants for the general population. Such study may help to develop nation-wide hospital guidelines for the prescribing of antidepressants in cancer patients and improve clinical outcomes in this vulnerable patient group.

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# List of Abbreviations

| | |
|---|---|
| AIHW | Australian Institute of Health and Welfare |
| ATC | Anatomical Therapeutic Classification |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disorder |
| GHQ | General Health Questionnaire |
| GBD | Global Burden of Disease |
| GORD | Gastro Oesophageal Reflux Disorder |
| HADS | Hospital Anxiety and Depression Scale |
| HREC | Human Research Ethics Committee |
| ieMR | integrated electronic Medical Record |
| LNR | Low and Negligible Risk |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| MAO | Monoamine oxidase |
| MAP | Medication Action Plan |
| MRN | Medical Reference Number |
| NICE | National Institute for Health and Care Excellence |
| NHMRC | National Health and Medical Research Council |
| NR | Not Report |
| NSAID | Nonsteroidal Anti-inflammatory Drugs |
| NSSA | Noradrenaline-serotonin specific antidepressant |
| OR | Odds Ratio |
| OTC | Over the Counter |
| PHQ | Patient Health Questionnaire |
| QUT | Queensland University of Technology |
| RBWH | Royal Brisbane Women's Hospital |
| SNRI | Serotonin–norepinephrine reuptake inhibitor |
| SPSS | Statistical Package for the Social Science |

| | |
|---|---|
| SSRI | Selective serotonin reuptake inhibitor |
| TCA | Tricyclic antidepressant |
| USA | United States of America |
| UK | United Kingdom |

# Statement of Original Authorship and Contribution

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

As a Master student, I was involved to fulfil the aims of literature review and research by conducting systematic literature review, meta-analysis, writing and submission of manuscript, and for the data extraction and collection, statistical analysis, results and writing of thesis.

I have received the acceptance of a manuscript for study 1 in the peer-reviewed journal Psycho-oncology.

QUT Verified Signature

Signature:

Date: 11.03.2016

# Acknowledgements

Firstly, I would like to thank my Principal Supervisor, Professor Monika Janda for her regular supervision, guidelines, and encouragements in every step of this research project. I hope her guidance will continue further with my future research project.

I would like to thank my Industry Supervisor, Kelly Mulvogue for providing me the support and regular collaboration in the hospital. I also want to thank my other Associate Supervisor, Dr Tracey DiSipio for guiding me in the literature review and meta-analysis methods.

I also would like to thank senior researchers from the Psycho-oncology Co-operative research Group (PoCoG) including Professor David Kissane, Dr Jeremy Couper, Professor Sallie Pearson, Dr Joanne Shaw for giving me the opportunity to work with them and their valuable comments and help to conduct the research at national level.

I wish to thank all the member of ihop group, especially Linda, Ngadiman, and Julie for helping me at various stage of this course. I sincerely appreciate the support of all the personnel from Department of Pharmacy, RBWH for helping me to continue my research.

I want to thank my family who lives abroad for their strong support and pray. Finally thanks to my husband, Saiful and son, Safir who were always with me and encourage me at every moment of this pathway.

# Chapter 1: Introduction

## 1.1 Depression in cancer patients

Cancer is a major reason for prolonged illness, disability and premature death (AIHW, 2012). More than 120,000 people are newly diagnosed with cancer each year in Australia (AIHW, 2015). Patients often face physical and psychological distress after a diagnosis of cancer; this distress often continues during the treatment procedures and throughout the survival period (NHMRC, 2003). However, many cases of depression remain unidentified. Sometimes health care professionals cannot easily detect the depression of cancer patients because it is difficult to differentiate the symptoms caused by the cancer or the treatment and mood disorders (Raison and Miller, 2003). Research has shown that continuation of untreated depression may cause risks for the survival of cancer patients (Faller et al., 1999, Olver and Burrows, 2007 & Hert et al., 2011).

Studies that reviewed the prevalence of depression in cancer patients showed that the prevalence of depression in cancer patients varies depending on cancer type and patients setting. A review of 46 studies (1966-2000) showed that the prevalence of major depressive disorder ranged from 5% to 26% diagnosed by the Hospital Anxiety and Depression Scale (HADS) (Hotopf et al., 2002). Another review during the same time period (1965-2002) of 92 studies on depression and type of cancer found that depression rate was highly associated with the type of cancer including oropharyngeal (22%–57%), pancreatic (33%–50%), breast (1.5%–46%), or lung (11%–44%) cancers (Massie, 2004). According to the patient setting and limitation of previous reviewed studies (including response rate of patients, quality of studies), a recent review which only included very high quality studies (n= 15, 1950-2012) showed that patients in palliative care (7%-49%) were diagnosed with higher prevalence rate of depression compared to other settings including inpatients (4%-14%), outpatients (5%-16%) or both (4%-11%) (Walker et al., 2012).

## 1.2 Prevalence of depression in cancer patients in Australia

Two large studies have been identified that aimed to determine the prevalence of depression in cancer patients in Australia. Both studies used the HADS in cancer patients which is a valid test to detect severity and caseness of depression (Bjelland et al., 2002). A large population based cross-sectional study was undertaken to determine the prevalence of

depression in long-term adult cancer survivors (≥5 years) diagnosed in 1997 and who survived after 2002 (Boyes et al., 2009). Of these, 4% (n= 35/863) were diagnosed with depression which was a similar level of depression to general population in Australia (Australian Bureau of Statistics, 1998). Another nationwide prospective cohort study from 2002-2006 in ovarian cancer showed that 5.9% (n= 47/798) of patients were suffering from depression (Price et al., 2010) which was somewhat higher than the general female population (5.1%, n= 50,790/995,900) in Australia (Australian Bureau of Statistics, 2008).

A number of studies (n= 3) showed that the prevalence of depression was high at the diagnosis of cancer and the following six months post diagnosis. Stafford et al. (2015) found that 33.3% (n= 35/105) of breast or gynaecologic cancer patients were diagnosed with depressive symptoms using the HADS and the prevalence rate of depression (22%, n= 23/105) decreased two years after diagnosis of cancer. Previously, Gallagher et al. (2002) identified that 43% (n= 84/195) of breast cancer patients reported the psychological distress two months and six months post-diagnosis of cancer using the General Health Questionnaire-12 (GHQ-12). In some instance, prevalence rate of depression changes with cancer treatment. A prospective observational study from 2008-2009 in people with head and neck cancers showed that 15% of patients (n= 15/102) faced mild to severe depression before cancer treatment which doubled (n= 30/102) after treatment determined by the HADS (Neilson et al., 2010). Overall, the findings of these studies in Australia showed the prevalence rate of depression appears to peak within 12 months of cancer diagnosis.

Another three studies conducted research on prevalence of depression of cancer patients according to their physical status. A large cohort study was conducted on adults (aged 45 years or older) in Australia 2006 to 2008 and 16.1% (n= 14,380/89,574) of the participants were cancer survivors. This study showed that cancer patients who needed help for daily tasks were at higher risk (Odds ratio (OR) 5.81; 95% Confidence Interval (CI) 4.88–6.91) of psychological distress diagnosed by the Kessler Psychological Distress Scale (K 10) compared to cancer patients without disability (1.14; 95% CI 1.04–1.24) (Banks et al., 2010). In palliative care, 45.8% (n= 121/266) of cancer patients were diagnosed with possible symptoms of depression determined by the HADS (O'Connor et al., 2010). Another study showed that cancer patients (n= 115) with emotional and physical problems were more likely to also be highly distressed as identified through routine distress screening measurement (Lee et al., 2010).

Overall, it has been identified that the prevalence of depression of cancer patients in Australia was high from the time of diagnosis of cancer to one year after the diagnosis of cancer.

### 1.3 Treatments of depression in cancer patients

European guidelines have been developed for the evidence-based management of depression of cancer patients in palliative care. The guidelines recommend the steps that should be followed in the prevention; detection, diagnosis and assessment; and treatment of depression (Rayner et al., 2011). In contrast, Australian and New Zealand Clinical Practice Guidelines for the treatment of depression by specialist services more generally (not specifically for cancer patients) summarises that it is necessary to consider assessment, treatment and management issues for the treatment of depression (Ellis et al., 2003 & Ellis, 2004). No specific guidelines for the treatment of depression in cancer patients are available in Australia. However, the following steps may be considered for the treatment of depression in cancer patients according to Australian and New Zealand Clinical Practice Guidelines-

#### *1.3.1 Assessment*

Before prescribing pharmacological therapy or medications, prescribers should check and identify risk factors of cancer patients including suicidal ideation or likelihood of harm to others; subtype, severity and duration of depression; family history and comorbidities of patients; availability or absence of social support, concurrent life stresses, chronic pain, and performance status (Ellis et al., 2003; Ellis, 2004 & Rayner et al., 2011).

#### *1.3.2 Treatment*

Four reviewed studies summarised the evidence of benefit of antidepressants for the improvement of psychological distress in cancer patients (Hennaux and Razavu, 1990; Raison and Miller, 2003; Laoutidis and Mathiak & 2013 Walker et al., 2014). Antidepressants should be used for moderate to severe depression and commonly act to reduce the symptoms of depression after two weeks of use. They should show the targeted level of therapeutic action within less than two months and need to continue to be taken for at least six months (Lu and Roughead, 2012 & Shultz and Malone, 2013). A recent systematic review of randomised controlled trials for the treatment of depression in cancer patients suggests that pharmacological therapy alone using antidepressants or in combination with psychological therapy may be effective in the treatment of depression in cancer patients (Walker et al., 2014).

### *1.3.3 Management*

Regular follow-up of patients by health care professionals is important to ascertain the treatment of depression is working at satisfactory level. Health care professionals need to monitor the side-effects of the medicines, the psychological status of patients and adherence to treatment of patients by regular check-ups (Ellis et al., 2003; Ellis, 2004 & López-Torres et al., 2013). According to the National Institute for Health and Care Excellence (NICE) guidelines in the UK, a 2-4 week interval for follow-up should be considered in the first three months and then longer intervals of monitoring depending on the improvement of depression for adult patients (NICE, 2014). A pre-post cohort study showed that an additional telephone call by a pharmacist or nurse within 2 weeks of newly administering antidepressants improved the rate of scheduled follow-up and visit attendance by patients from 7% to 24% (Gallimore and Kushner, 2013).

## 1.4 Prescription practices of antidepressants to cancer patients in Australia

According to the National Health and Medical Research Council (NHMRC) clinical practice guidelines in Australia, use of antidepressants can improve the mental distress of cancer patients (NHMRC, 2003). However, the use of medications for the treatment of depression or anxiety may have decreased over time in Australia. The National Mental Health and Wellbeing survey showed that 1.8 million people in Australia suffered from a minimum of one 12-month affective mental disorder; whereas less than half of them took services for mental health treatment and the majority of them used services from a general practitioner (Australian Bureau of Statistics, 2008). Another National Health Survey in Australia (n= 48,359) revealed that the prevalence of psychological distress decreased from 4.8% to 4.3% for cancer patients and 3.7% to 3.6% for non-cancer patients from 2001 to 2008. Similarly, the use of antidepressants by cancer patients for the treatment of psychological distress declined from 11.2% to 6.2% over the same 8 years (Atlantis et al., 2012). Given that depression rates are unlikely to have decreased, this could be due to underreporting or could indicate that cancer patients may not have sufficient access to adequate supportive care or that clinicians find it difficult to diagnose depression in cancer patients (somatic features of depression are very similar to cancer/treatment effects; difficulty to separate disorder from ‘sadness’). Therefore it is a major issue to consider the prescription practices of antidepressants for cancer patients and their regular follow-up in Australia.

Various health professionals including physicians, oncologists, or psychiatrists may prescribe antidepressants to cancer patients. According to the Australian Institute of Health and Welfare, physicians prescribe 86% of antidepressants for the treatment of mental health in general, whereas psychiatrists prescribe only 8% and non-psychiatrists 6% of antidepressant medicines (AIHW, 2012). There is also variation in doses of antidepressants prescribed by providers to the depressive patients. Usually it has been identified that psychiatrists provide higher doses of antidepressants compared to general practitioners in Australia (McManus et al., 2003). However, it is not known which group of health care professionals prescribe most frequently to cancer patients comorbid with depression, what the dose of antidepressants is, how long patients take the medications, whether it has the desired benefit, whether the follow-up regimen is similar to what is recommended for mental health symptoms in people without cancer, and whether this follow-up is adequate.

### 1.5. Studies conducted on prescription of antidepressants to cancer patients in Australia

Only one population-based cohort study was identified in Australia conducted between 2005-2009 on cancer patients taking antidepressants (Pearson et al., 2015). Dispensing records was the main data source of information about antidepressants. This recent cohort study was conducted to assess the effect of a cancer diagnosis on prevalence and the timing of starting antidepressants. 17.2% (n= 995/5795) of cancer patients initiated antidepressants for the treatment of depression. The highest rate of treatment starting was from 12 weeks before to 16 weeks after cancer diagnosis, while half of patients discontinued the antidepressants before 16 weeks of follow-up. Selective serotonin reuptake inhibitors (SSRIs) (47%, n= 467/995) followed by tricyclic antidepressant (TCA) (33%, n= 328/995) was the commonly prescribed antidepressants and durations of treatment were shorter than recommended for depression (Pearson et al., 2015). This study did not analyse the prescription characteristics or practices by health care professionals, potential side effects or drug-drug interactions.

Another cohort study of Australian military veterans (Lu and Roughead, 2012) was conducted on the persistent of antidepressant use by patients and reasons to cease the treatment. This study showed that cancer patients (n= 4,130/28,585) were at high risk of mental health impact due to higher rate of ceasing antidepressants before a six months course was completed compared to other chronic diseases patients such as those with diabetes, cardiovascular disease, or respiratory conditions. A recent multinational study which was identified in the literature search undertook research in eight different countries, including

Australia (n=70), and examined the use of antidepressants in advanced cancer patients (Janberidze et al., 2014). Overall, lack of follow-up after providing prescription of antidepressant to the cancer patients resulting in discontinuation of depression treatment was found from the previous studies. However, no individual analysis on the prevalence of antidepressants in participating cancer patients from Australia was provided.

Overall, there is a serious shortage of research on this topic in Australia. Particularly there is no significant study analysing the current prescribing practices for antidepressants in cancer patients in Australia.

### 1.6 Knowledge gaps

No literature review has been identified on the prescription practices of antidepressants to cancer patients. There is no information about what type and dose of antidepressants prescribed to the cancer patients, who prescribed these medicines, follow-up of antidepressants after providing to the patients.

In the Australian context, there is a significant knowledge gap in this area. No cross-sectional, prospective cohort, case-control or intervention study has been identified on the prescription practices of antidepressant to cancer patients. It is unknown which professional group (psychiatrist, medical oncologist, surgeon, pain specialist, general practitioner) most commonly prescribes antidepressants (type, dose, indication, change of medicines), whether patients are followed up about the benefit of the prescription, how long patients take these medicines, or why they are discontinued.

A systematic review of existing literature in both Australia and worldwide is needed to determine the prescription practice of antidepressant to cancer patients in Australia before conducting further research. This review will help to identify the overall prevalence rate of antidepressants to cancer patients across the world and also to determine whether prescription prevalence varies depending on the study or patient characteristics. In addition, a systematic review of studies will also help to outline the suitable research methods and data collection procedures for future research in this area in Australia.

## 1.7 Thesis outlines

To consider the lack of research and significant knowledge gaps on prescription of antidepressants to cancer patients, the current thesis, therefore had two main aims to be addressed in two studies:

### *1.7.1 Study one: A systematic review and meta-analyses*

1. To describe the proportion of cancer patients who are prescribed antidepressants;

2. To determine whether prescription prevalence varies depending on the study methodology or patient characteristics;

3. To review the characteristics of antidepressants in each study according to study and data collection method.

This study was designed to provide the following outcomes important for public health practice including-

1. Overall pooled estimate of prescription prevalence of antidepressants to cancer patients from the published sources;

2. Pooled estimate of prevalence of antidepressants to cancer patients according to study and patient characteristics;

3. Type and dose of antidepressants prescribed by the health care provider;

4. Trends of prescription of antidepressants over time;

5. Follow-up of antidepressants after providing prescription.

The literature was systematically searched according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method using the keywords, 'antidepressants', 'prescription', 'psychotropic' and 'cancer' in the databases of PubMed, Embase, Web of Science, Scopus and psychINFO. The comprehensive meta-analysis software (Version 3 by Borenstein, Biostat, Englewood, New Jersey, US, 2015) was used for the quantitative analysis of the obtained literature data. The article resulting from this review was accepted in the peer-reviewed journal 'Psychooncology'.

### *1.7.2 Study two: A retrospective case-control study*

A retrospective, matched case-control study of antidepressants prescription in inpatients with or without cancer was conducted which aimed:

1. To describe the sociodemographic and clinical characteristics of cancer inpatients and non-cancer inpatients prescribed antidepressants;
2. To compare the antidepressants profile of these inpatients with cancer and an age and gender-matched sample without cancer;
3. To determine the occurrence of adverse effects or potential drug-drug interactions of antidepressants with other medicines prescribed to cancer patients.

This study was designed to address the following results important for public health practice including-

1. Describe the characteristics of cancer and non-cancer patients who received antidepressant as inpatients, and their prescription profile including type, dose and prescriber;

2. Differences in the characteristics of antidepressant prescriptions in cancer patients compared to non-cancer inpatients.

This study was conducted by extracting prescription data from the clinical records and medicine records of 75 randomly selected inpatients within the first 12 months after diagnosis of cancer currently undergoing cancer or post-cancer treatment at Royal Brisbane Women's Hospital, and 75 controls without cancer matched to the cancer patients by age and gender. This allowed ascertaining whether similar antidepressants were taken by cancer patients, the indication for this prescription, and the prescribers.

## 1.8 Funding

There was no funding involved in this project.

# Chapter 2: A systematic review and meta-analysis

A systematic review and meta-analysis was conducted at the starting point of thesis to determine the pooled estimate of prevalence of antidepressants to cancer patients and knowledge gaps of current studies.

## 2.1 Background

Globally cancer is one of the main contributors to the burden of disease and mortality (GBD 2013 Mortality and Causes of Death Collaborators et al, 2015). Cancer patients commonly suffer from pre-existing or acquired co-morbidities including mental health problems (Hert et al., 2011). Mehnert *et al.* (2014) estimated that the four-week prevalence of mental health disorders in cancer patients is 31.8% (n=679/2,140) (Mehnert et al., 2014). In patients with advanced cancer, or those requiring palliative care, the prevalence rate of depression has been reported to be 15%-28% (Hotopf et al., 2002 and Walker et al., 2012).

Antidepressants are widely prescribed for the pharmacological treatment of mental health disorders and some studies report that antidepressant prescription has increased over the last three decades (Helgason et al., 2004; Moore et al., 2009; Pratt et al., 2011 & Stephenson et al., 2012). According to the World Mental Health Survey (n=66,387) conducted in 24 countries, the prevalence may vary widely between countries, and between cancer types, and many cancer patients may require yet not receive treatment for depression (Nakash et al, 2014). Due to high symptom burden, patients themselves as well as health care professionals may fail to recognise depression, further increasing the treatment gap (Greenberg, 2004 & Gouveia et al., 2015). This is problematic because continuing untreated depression of cancer patients may cause increased hospitalisations, non-adherence to cancer treatments and shorter survival (Valente and Saunders, 1997, Pasquini and Biondi, 2007; Kissane, 2009 & Satin et al., 2009).

While antidepressants may improve symptoms of depression, they also have side effects and can interact with cancer medications (Gøtzsche, 2014). For example, selective serotonin reuptake inhibitors (SSRIs) may reduce the efficacy of Tamoxifen, commonly prescribed in breast cancer treatment (Jaiyesimi et al., 1995; Onitilo et al., 2006 & Caraci et al., 2011). Furthermore, research has raised the possibility that some patients may receive antidepressants unnecessarily, while those on prescriptions may not be optimally followed

(Coyne et al., 2004; Janberidze et al., 2014 & Zhao et al., 2014). Regular follow-up of psychological status, adherence to treatment, potential drug-drug interactions or side-effects is clearly important (Ellis et al., 2003; Ellis, 2004; Trill, 2012 & López-Torres et al., 2013). One of the reasons for unwarranted prescription or lack of follow-up may be that many different medical specialities are involved in a cancer patients' treatment. Thus the coordination of treatment for cancer co-morbidities for which antidepressants may also be prescribed, including pain, fatigue, anorexia, hormonal dysregulation or insomnia, is complex.

A systematic review and meta-analysis was therefore undertaken to describe the proportion of cancer patients who are prescribed antidepressants; whether prescription varies depending on the place of study or study methodology; cancer type and stage; patient age and sex; timing related to diagnosis or death; whether studies report on the type, dose, prescriber and follow-up including monitoring of adverse side-effects or drug-drug interactions; duration of taking antidepressants and how many prematurely discontinue the treatment.

## 2.2 Methods

### *2.2.1 Search Strategy*

A systematic search of the published literature from 1979 (Earliest relevant article found) to February 2015 followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. We searched five databases (PubMed, Embase, Web of Science, Scopus, and psychINFO); the search strategy and time period covered by each of the databases is listed in Table 2.1.

***Table 2.1 Search strategy used in the different databases***

| Name of Database | Searched Terms | Timeline showed during searching databases |
|---|---|---|
| PubMed | cancer AND "Psychotropic Drugs"[Mesh] and prescription and "Antidepressive Agents"[Mesh] | Aug 1979- Feb 2015 |
| Embase | Antidepressant, prescription, cancer, Psychotropic | Nov 1979- Jan 2015 |
| Web of Science | Psychotropic and cancer and prescription and antidepressants | Feb 1990-Oct 2014 |
| Scopus | Psychotropic and cancer and prescription and antidepressants | Nov 1979-Dec 2014 |
| psychINFO | psychotropic drug AND cancer AND prescription AND antidepressants | Mar 2004- Apr 2013 |

The main Medical Subject Heading (MeSH) terms used were: 'psychotropic', 'antidepressants', 'prescription', AND 'cancer'. The bibliographies of relevant articles were also searched manually and relevant additional references included if they fulfilled the inclusion criteria (Figure 2.1).

### *2.2.2 Inclusion and Exclusion Criteria*

Patient, outcome and study design criteria were: adult cancer patients or adult survivors of childhood cancer (studies of childhood cancer or adolescents younger than 18 years were excluded); article reports the proportion of cancer patients who were prescribed antidepressants to improve symptoms of depression. We excluded articles that researched antidepressants as a risk factor for cancer or cancer mortality; or where the antidepressants were used for management of symptoms other than depression. We included observational cohort, cross-sectional or case-control studies published in English. We excluded clinical trials of antidepressant efficacy, review articles or editorials. If several articles were based on the same dataset only the most detailed or most recent article was included to avoid repeated use of the same data. One study reported on three independent cross-sectional surveys at three different time points (Farriols et al., 2012), all three datasets were included separately in the meta-analysis. For relevant conference abstracts where no full article could be found, we contacted the authors to ask for the status of the publication. If the authors did not reply, we included data from the abstract only where it reported at least the proportion of cancer patients taking antidepressants.

### *2.2.3 Data extraction*

The main characteristics of the studies used for sub-group analysis are presented in Table 2.2, including type, place and decade of study; source of prevalence data (i.e. prescription record; patient self-reporting questionnaire or interview; medical chart, or cancer registry; health care professionals reporting questionnaire; or dispensing record); patient age range and gender; cancer type and stage. Supplementary Tables 2.1 and 2.2 show sensitivity analyses of the main results when excluding studies with the highest or lowest prevalence, or grouping studies by full decades, respectively. Table 2.3 summarises in detail the reviewed studies in alphabetical order by first author's surname, divided into cross-sectional, case-control (data extracted for cancer cases only) or cohort studies (last reported time-point used). Further data extracted included: duration of study; sample size; patient average/median age; sample

setting; who prescribed antidepressants; prevalence rate of antidepressants; type, and number of antidepressants (Table 2.3).

### *2.2.4 Quality assessment and bias risk*

Quality and risk of bias (Table 2.3) were assessed by two scorers independently (MJ, SS). Quality included sample size; selection of sample according to study method; study design; presence of detail information of antidepressants. Bias included recruitment approach and non-response rate; completeness of medication data collection; and result reporting. Each scorer rated each study on a scale ranging from 1-4 for quality and 0-4 for bias (Mitchell et al., 2011) (Supplementary Table 2.3), average scores were used if disagreement was 1 point only; larger disagreements were resolved by discussion.

### *2.2.5 Statistical Analysis*

Comprehensive Meta-Analysis (Version 3 by Borenstein, Biostat, Englewood, New Jersey, US, 2015) was used to calculate the prevalence rate and 95% CI overall, and by subgroups listed in Table 2.2.

Heterogeneity was determined by Q and $I^2$ values and >50% was considered as severe heterogeneity (Higgins et al., 2003). Publication bias was determined by using Begg's funnel plot of standard error against logit event rate (Egger et al., 1997). Given that high heterogeneity was detected, we repeated the analyses after excluding studies which used data based on patient self-report, and studies with the highest and lowest prevalence rates from the overall result, and observed whether this made a >5% difference to the prevalence rate, however results remained largely unchanged.

## 2.3 Results

Overall 1,537 articles were found through the systematic (n=1,520) and manual (n=17) search. Figure 2.1 shows the PRISMA flow-diagram of screened and selected full-text articles.

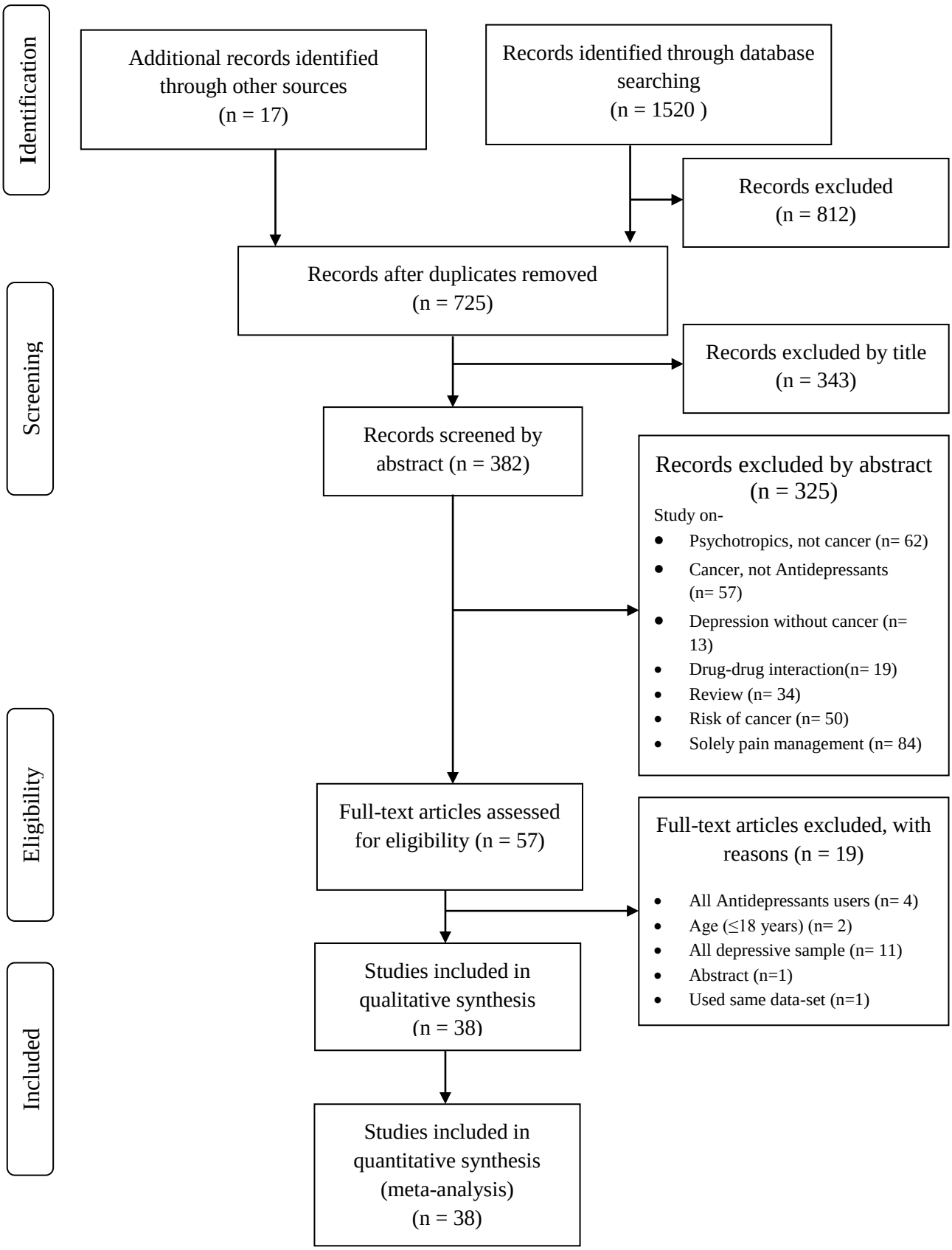


***Figure 2.1: PRISMA flow diagram of systematic review and meta-analysis***

After excluding duplicates (n=812) and irrelevant studies (n=343), 382 articles remained. Irrelevant studies reported on biomedical or laboratory markers of depression, antidepressants prescribed to the general population, as risk factors for mortality of cancer patients, or use for pain, sleep disturbances or fatigue (Figure 2.1). Next 325 of the remaining 382 articles were excluded because on further review they did not fulfil the inclusion criteria, while 57 articles were read in full-text including three conference abstracts. Of these, 19 articles did not provide the required data for extraction. Therefore, 38 articles remained for meta-analysis.

### *2.3.1 Overall prevalence*

Of 300,179 cancer patients included in the meta-analysis, 47,391 were prescribed antidepressants. Across all studies the pooled estimated prevalence of antidepressants prescribed was 15·6% (95% CI= 13.3-18.3), ranging widely from 0.5%-67% (Figure 2.2).

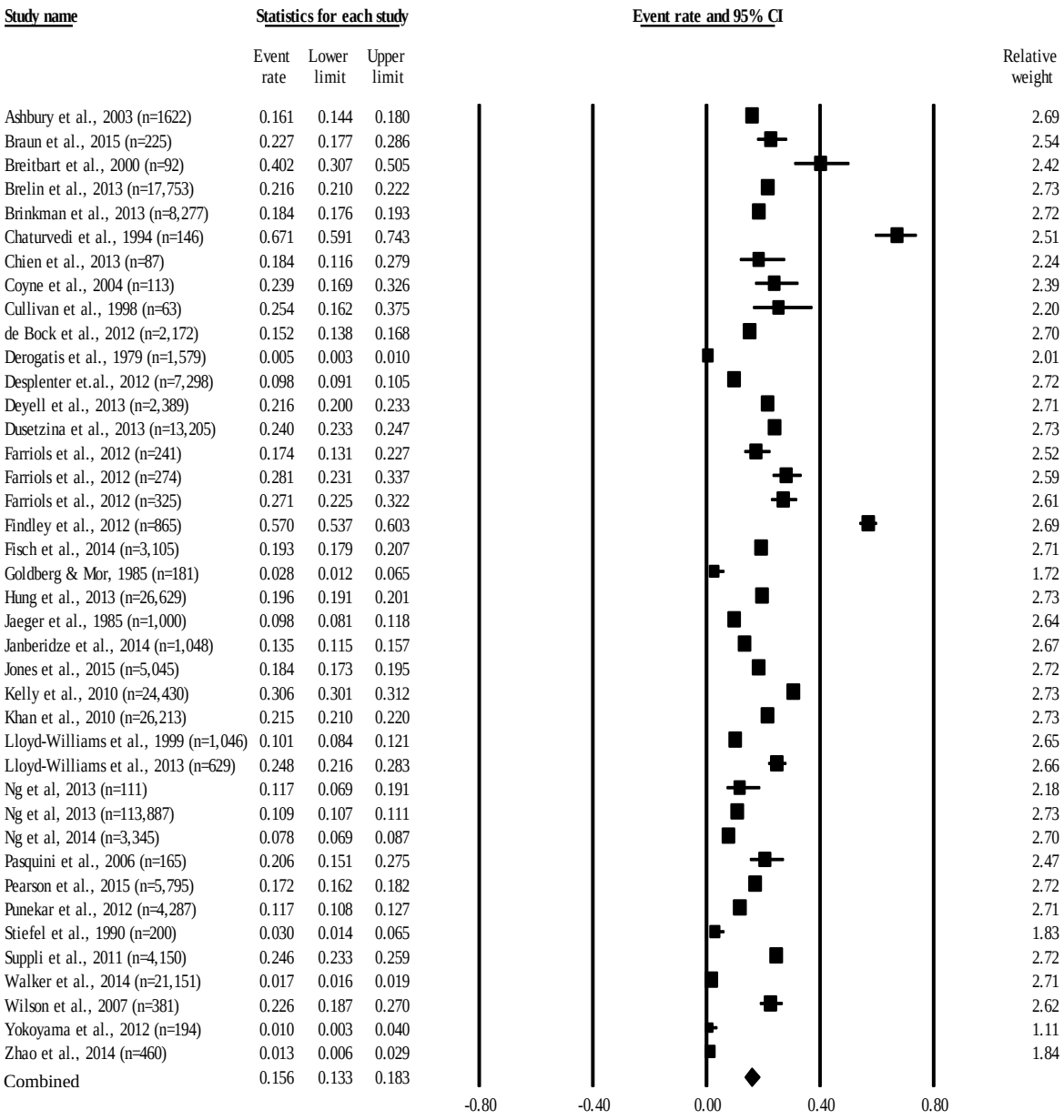


***Figure 2.2: Weighted antidepressant prevalence rates***

### *2.3.2 Association of antidepressant prescribing with subgroup characteristics*

Prescribing prevalence was lower in cross-sectional (n=18, 12.5%, 95% CI= 10.1-15.4) compared to cohort studies (n=16, 19.6%, 95% CI= 16.2-23.5) (Table 2.2).

***Table 2.2: Characteristics and sub-group analysis of study and sample***

| Characteristics | | Number of studies (n=38) | Prevalence (95%CI) | Heterogeneity ($I^2$) |
|---|---|---|---|---|
| **Study Characteristics** | Study Method | | | |
| | All studies | 38 | 15.6% (13.3-18.3) | 99.67 |
| | Cross-sectional | 18 | 12.5% (10.1-15.4) | 99.47 |
| | Cohort | 16 | 19.6% (16.2-23.5) | 99.12 |
| | Case-control | 4 | 14.5% (9.7-21.2) | 99.02 |
| | Place of the study | | | |
| | North America | 17 | 16.5% (12.9-20.9) | 99·18 |
| | Europe | 14 | 17.1% (13.1-22) | 99.76 |
| | Asia | 5 | 7.4% (4.3-12.5) | 99.76 |
| | Australia | 1 | 17.2% (6.2-39.5) | |
| | Multinational | 1 | 13.5% (4.6-33.2) | |
| | Decades according to year of publication | | | |
| | 1971-1980 | 1 | 0.5% (0.1-1.8) | |
| | 1981-1990 | 3 | 5.0% (2.5-9.7) | 87.50 |
| | 1991-2000 | 4 | 32.0% (21.1-45.3) | 98.65 |
| | 2001-2010 | 6 | 22.3% (15.5-30.9) | 99.20 |
| | ≥2011 | 24 | 15.0% (12.4-18.1) | 99.67 |
| | Data collection method | | | |
| | Prescription record | 20 | 15.6% (12.5-19.3) | 99.02 |
| | Patient self-reporting questionnaire/ Interview | 7 | 18.4% (12.4-26.5) | 99.23 |
| | Medical chart/ Cancer registry | 6 | 15.3% (9.9-22.8) | 99.58 |
| | Health care professionals reporting questionnaire | 3 | 10.9% (5.7-19.7) | 95.01 |
| | Dispensing report | 2 | 11.7% (5.6-22.8) | 99.33 |
| **Sample Characteristics** | Average/Median age | | | |
| | 25-34 | 1 | 21.6% (7.3-48.9) | |
| | 35-44 | 1 | 19.6% (6.6-45.8) | |
| | 45-54 | 3 | 8.1% (3.8-16.5) | 99.27 |
| | 55-64 | 12 | 13.7% (9.9-18.7) | 99.47 |
| | 65-74 | 11 | 16.5% (11.9-22.5) | 99.77 |
| | 75-84 | 2 | 17.8% (8.2-34.3) | 63.90 |
| | Not specified | 8 | 16.7% (11-24.4) | 99.19 |
| | Gender | | | |
| | Females only | 6 | 22.6% (16-31) | 99.46 |
| | Both | 29 | 15.1% (12.7-17.9) | 99.59 |
| | Not specified | 3 | 5.7% (2.7-11.6) | 92.52 |
| | Cancer type | | | |
| | Single type[1] | 7 | 22.1% (16-29.7) | 99.35 |
| | 2-4 types[2] | 4 | 18.8% (12.1-27.9) | 94.15 |
| | Any | 27 | 13.5% (11.2-16.2) | 99.52 |
| | Cancer stage | | | |
| | Cured or remission | 1 | 22.7% (8-49.8) | |
| | Any stage | 11 | 12.6% (9-17.2) | 99.66 |
| | Advanced/ Terminal stage | 11 | 16.1% (12.3-20.8) | 95.76 |
| | Not reported | 15 | 15.8% (12-20.5) | 99.76 |

[1]Single type included breast (n=6; 22·6%; 95% CI= 16.0-30.9) or pancreatic cancer (n=1; 18.4%; 95% CI= 6.6-41.8). [2]2-4 types included breast, colon, lung, prostate cancer

Studies conducted in Asia (n=5) showed lower prevalence rates (7.4%, 95% CI= 4.3-12.5) compared to studies from other continents (Table 2.2). Two studies in Asia identified only a 1 to 1.3% prevalence rate (Yokoyama et al., 2012 & Zhao et al., 2014). Zhao *et al.* (2014) reported that while the one-month prevalence of depressive disorder was 25% (n=119/460), only six patients were prescribed antidepressants (Zhao et al., 2014).

Prevalence rates between studies differed depending on the source of data, with highest rates from patient self-reporting questionnaire or interviews (18.4%, 95% CI= 12.4-26.5) and lowest from physician-reported questionnaires (10.9%, 95% CI= 5.7-19.7), or dispensing reports (11.7%, 95% CI= 5.6-22.8) (Table 2.2).

Few patient characteristics were associated with prescription practices, and no clear pattern emerged with regards to cancer stage; however, compared to other cancer patients, women and those with breast cancer were more commonly prescribed antidepressants (Table 2.2). There was a u-shaped association between age group and prescribing prevalence.

Prescription details are summarised in Table 2.3, twenty one studies presented the type or name of the antidepressants. Among these studies, SSRIs were most commonly prescribed. Nine articles detailed the full range of antidepressants (Chaturvedi et al., 1994; Lloyd-Williams et al., 1999; Pasquini et al., 2006; Kelly et al., 2010; de Bock et al., 2012; Brelin et al., 2013; Lloyd-Williams et al., 2013 & Pearson et al., 2013). In some instances, cancer patients received more than one type of antidepressant (Chaturvedi et al., 1994; Kelly et al., 2010 & Deyell et al., 2013) or the type of antidepressant changed over the course of cancer treatment (Pearson et al., 2013).

*Table 2.3: Studies reporting prevalence of antidepressant prescriptions to cancer patients*

| Study | Quality | Bias Risk | Place of study | Duration of study | Sample size | Average/ Median age | Gender | Cancer Type | Cancer Stage | Sample setting | Who prescribed antidepressant | Prevalence of Antidepressant | Types & number of antidepressant taking by cancer patients |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cross sectional studies** | | | | | | | | | | | | | |
| **Antidepressants prescription data reported from prescription record** | | | | | | | | | | | | | |
| Ashbury et al., 2003[29] | 3 | 2.5 | USA | Nov 1999-Nov 2001 | 1622 | Average 64.7 | M(n=435/1622) F(n=1187/1622) | Breast(n=850/1622), Colon(n=299/1622), Lung(n=473/1622) | Any stage | Community Oncology Practice | Oncologist | 16% (n=261/ 1,622) | NR |
| Coyne et al., 2004[21] | 3.5 | 3 | USA | NR | 113 | NR | Only F(n=113) | Breast (n=113) | Stage 1 (n=24/113) Stage 2a (n=31/113) Stage 2b (n=27/113) Stage 3a (n=11/113) Stage 3b (n=9/113) Stage 4 (n=11/113) | Waiting Room sample | NR | 24%(n=27/113) | NR |
| Cullivan et al., 1998[30] | 2 | 3 | Ireland | 1997(July-Dec) | 63 | NR | M(n=15/63) F(n=48/63) | Any type | Any stage | Inpatient | Oncologist, General Practitioner, Psychiatrist | 26%(n=16/63) | Type: SSRI-Nefazodone & other |
| Derogatis et al., 1979[31] | 2.5 | 2.5 | USA | 1977(April-Sep) | 1,579 | Average age 54 | M(n=631/1,579) F(n=948/1,579) | Any type | NR | Inpatient, Outpatient | NR | 0.5%(n=8/1,579) | Type: TCA-Amitriptyline, Imipramine |
| Farriols et al., 2012[28] | 2.5 | 2.5 | Spain | 2002 | 241 | Average age 69.7 | M(n=161/241) F(n=80/241) | Any type | Advanced cancer | Palliative care | Psychiatrist | 17%(n=42/241) | Type: Paroxetine(n=23/42) Amitriptyline (n=8/42), Fluoxetine(n=6/42), Citalopram(n=4/42), Trazodone(n=1/42) |
| | | | Spain | 2006 | 274 | Average age 71.6 | M(n=170/274) F(n=104/274) | | | | | 28%(n=77/274) | Type: Mirtazapine (n=35/77), Citalopram (n=33/77), Paroxetine (n=11/77), Venlafaxine (n=7/77), |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | Amitriptyline (n=3/77), Fluoxetine(n=3/77), Duloxetine(n=1/77), Others(n=2/77) |
| | | | Spain | 2009 | 325 | Average age 72.2 | M(n=196/325) F(n=129/325) | | | | | 27%(n=88/325) | Type: Mirtazapine (n=30/88), Escitalopram (n=23/88) Citalopram (n=15/88), Paroxetine(n=8/88), Amitriptyline (n=7/88), Trazodone(n=7/88), Duloxetine(n=6/88), Venlafaxine (n=5/77), Fluoxetine(n=1/88), Others(n=5/88) |
| Jaeger et al., 1985[32] | 3 | 1.5 | USA | Jan 1981-Feb 1982 | 1000 | Average age 68.2 | M(n=550/1000) F(n=450/1000) | Any type | NR | Inpatient | Physician, Psychiatrist | 10%(n=98/1000) | Type: Amitriptyline, Imipramine |
| Lloyd-Williams et al., 1999[33] | 2.5 | 1.5 | UK | 1995(Jan-Dec) | 1046 | Average age 61.3 | NR | Any type | Terminal cancer | Palliative care | Psychiatrist | 14.6% (n=153/1046) | Type: TCA-24.5%, SSRI-71.8%, MOA-1.9% Dothiepin-25mg/day, Fluoxetine, Paroxetine, Sertraline, Flupenthixol, Phenelzine |
| Punekar et al., 2012[34] | 3 | 1.5 | USA | 2001-2006 | 4287 | NR | M(n=1691/4287) F(n=2596/4287) | Any type | NR | Cancer survivor | NR | 11.7% (n=503/4287) | NR |
| **Antidepressants prescription data reported from medical record/ chart & cancer registry** | | | | | | | | | | | | | |
| Breitbart et al., 2000[35] | 3 | 2 | USA, | Jun 1998-Jan 1999 | 92 | Average age 65.9 | M(n=37/92) F(n=55/92) | Any type | Terminal cancer | Inpatient | NR | 40%(n=37/92) | NR |
| Chien et al., 2013[36] | 1.5 | 2 | Taiwan | 2010 | 87 | NR | NR | Pancreatic cancer | Advanced cancer | NR | NR | 18·4%(n=16/87) | NR |
| Chaturvedi et al., 1994[37] | 2.5 | 2 | UK | NR | 146 | Average age 49 (19-83) | M(n=46/146) F(n=100/146) | Any type | NR | Inpatient, Outpatient | Psychiatrist | 67%(n=98/146) | Type: Dothiepin(n=74/110)-25-225mg, Mianserin(n=13/110)-10-30mg, Amitriptyline(n=9/1 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | 10)-50-175mg, Clomipramine(n=5/110)-50-150mg Other-(n=9/110) Number: One (n=86/98), Two (n=12/98), Total number of prescription, n=110 |
| Walker et al., 2014[38] | 4 | 1.5 | UK | 2008-2011 | 21151 | Average age 64.4 | M(n=6039/21151) F(n=15112/21151) | Breast (n=8461/21,151), Lung (n=4316/21,151), Colorectal (n=3355/21,151), Genitourinary (n=2009/21,151), Gynaecological (n=3010/21,151) | NR | Outpatient | Psychiatrist | 1.75% (n=370/21151) | Type: Amitriptyline, Citalopram, Clomipramine, Dosulepin, Doxepin, Duloxetine, Escitalopram, Fluoxetine, Flupentixol, Fluvoxamine, Imipramine, Lofepramine, Mirtazapine, Nortriptyline, Paroxetine, Phenelzine, Reboxetine, Sertraline, Trazodone, Trimipramine, Venlafaxine. |
| Zhao et al., 2014[23] | 2.5 | 2.5 | China | 2013(March-Sep) | 460 | Average age 59.4 | M(n=226/460) F(n=234/460) | Any type | Any stage | Inpatient | Psychiatrist, Oncologist | 1.3% (n=6/460) | NR |
| **Antidepressants prescription data reported from health care professionals reporting questionnaire** | | | | | | | | | | | | | |
| Janberidze et al., 2014[22] | 3.5 | 1.5 | Norway Austria Italy Switzerland England Australia Canada Germany | Oct 2008-Dec 2009 | 1048 | Average age 62·5 | M(n=540/1048) F(n= 508/1048) | Any type | Advanced cancer | Inpatient, Outpatient | NR | 14% (n=141/1048) | NR |
| Stiefel et al., 1990[39] | 3 | 1.5 | USA | Dec 1987 | 200 | Average age 52 | NR | Any type | NR | Inpatient | Physician | 3%(n=6/200) | Type: Amitriptyline, Desipramine, Maprotiline |
| **Antidepressants prescription data reported from self-reporting questionnaire/ interview** | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Findley et al., 2012[40] | 3.5 | 2.5 | USA | 2000-2005 | 865 | NR | M(n=593/865) F(n= 272/865) | Any type | NR | Medicare Current Beneficiary | NR | 57%(n=493/865) | Type: MAO SSRI SNRI TCA |
| Goldberg & Mor, 1985[41] | 2.5 | 2.5 | USA | NR | 181 | NR | M(n= 96/181) F(n= 85/181) | Any type | Terminal cancer | Hospice sample | NR | 2.76%(n=5/181) | SSRI/SNRIs Doxepine, Amoxapine, Amitriptyline, Imipramine |
| Yokoyama et al., 2012[42] | 1.5 | 3.5 | Japan | 2010(June-Dec) | 194 | NR | NR | Hematological, Esophageal, Gastric, Pancreatic, Colon, Lung, Breast, Ovarian, Uterine, Skin | NR | Outpatient | NR | 1%(n=2/194) | NR |
| **Case-control studies** | | | | | | | | | | | | | |
| **Antidepressants prescription data reported from prescription record** | | | | | | | | | | | | | |
| Desplenter et.al., 2012[43] | 3 | 1.5 | UK | 2005-2010 | 7298 | Average age 67.8 | M(n=3595/7298) F(n=3703/7298) | Breast(n=1547/7298) Colorectal (n=1270/7298), Lung(n=1299/7298), Prostate (n=1058/7298), Upper GI (n=540/7298), Melanoma (n=402/7298), Gynaecological (n=445/7298) Urological (n=737/7298) | NR | General Practice | General Practitioner | 9.8% (n=713/7298) | Type: TCA, Other |
| Jones et al., 2015[44] | 2.5 | 1.5 | USA | 2005-2011 | 5045 | Average age 77 | M(n=2686/5045) F (n=2359/5045) | Prostate (n= 2686/5045), Breast (n=2359/5045) | NR | NR | NR | 18.4%(n=928/ 5045) | Type: SSRI, SNRI, TCA, MAO |
| Ng et al, 2013b[45] | 3 | 1 | Netherland | Jan 2006-Dec 2008 | 113887 | Average age 60.45 | M(n=42594/ 113887) F(n=71293/ 113887) | Any type | Any stage | Health insurance company | NR | 10·9% (n=12414/113887) | NR |
| **Antidepressants prescription data reported from self-reporting questionnaire/ interview** | | | | | | | | | | | | | |
| Braun et al., 2015[46] | 3 | 2.5 | USA | NR | 225 | Average age 59.5 | M(n= 80/225) F(n= 135/225) | Any type | Cure/ remission stage | National Comorbidity Study | Psychiatrist Physician | 22.6% (n=51/225) | NR |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Replication | | | |
| **Cohort studies** | | | | | | | | | | | | | |
| **Antidepressants prescription data reported from prescription record** | | | | | | | | | | | | | |
| Brelin et al., 2013[47] | 3.5 | 3.5 | Norway | Jan 2005-Dec 2006 | 17753 | Average age 71.9 | M(n=9617/17753) F(n=8136/17753) | Any type | Terminal stage | Norwegian Prescription Database | General Practitioner Physicians with no registered specialty Internists surgeons Oncologist Psychiatrist | 22% (n=3836/17753) | Type: TCA-21%(n=816/3836), SSRI-56%(n=2131/3836), TeCA-19%(n=717/3836), MAOI-<1%(n=7/3836), SNRIs 4% (n=145/3836), Other-<1%(n=20/3836) Citalopram Escitalopram Mianserin Mirtazapine |
| de Bock et al., 2012[48] | 3 | 3 | Netherland | 1994-2006 | 2172 | Average age 62 | Only F(n=2172) | Breast(n=2172) | NR | Prescription data | General practitioner | 15% (n=331/2172) | Type: Amitriptyline (n=144/331) Paroxetine (n=66/331) Venlafaxine (n= 38/331) Citalopram (n= 25/331) Mirtazapine (n= 19/331) Others(n=39/331) |
| Deyell et al., 2013[49] | 3 | 3 | Canada | Jan 2001-Dec 2004 | 2389 | Average age 28.3 | M (n=1225/2389), F (n=1164/2389) | Any type | NR | BC Cancer Registry | NR | 21.6%(n=515/2389) | Type: MAO, SSRI Serotonin modulators TCA, Other Number: One (n=346), ≥Two(n=169) |
| Dusetzina et al., 2013[50] | 2.5 | 2.5 | USA | July 2004-Dec 2009 | 13205 | Average age 60.5 | Only F (n= 13205) | Breast(n=13205) | NR | Inpatient, Outpatient | Oncologist Primary carer Oncologist Primary carer | 24% (n=3169/13205) | NR |
| Hung et al., 2013[51] | 2.5 | 2.5 | Taiwan | Jan 2000-Dec 2005 | 26629 | Median age 44 | Only F(n=26629) | Breast(n=26629) | Early & advanced stage | Inpatient, Outpatient, Emergency | NR | 19.6% (n=5223/26629) | NR |
| Kelly et al., 2010[52] | 3.5 | 0.5 | Canada | 1993-2005 | 24430 | Median age 74 | NR | Breast(n=24430) | NR | Cancer Registry | NR | 31% (n=7483/24430) | Type: SSRI (56%,n=4190/7483), SNRI |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | Paroxetine(n=1938), Sertraline(n=1872), Citalopram(n=1762) Venlafaxine (n=1205), Fluoxetine-(n=994) Fluvoxamine- (n=772) Number: One (n=3974/7483), Two (n=2582/7483), Three (n=927/7483) |
| Khan et al., 2010[53] | 2.5 | 2.5 | UK | 2003-2006 | 26213 | Average age 72.36 | M (n=6805/26213) F(n= 19437/26213) | Breast (n=16773), Colorectal (n=4982), Prostate (n=4458) | Any stage | General Practice Research Database | General Practitioner | 21.5% (n=5638/26213) | NR |
| Ng et al, 2013-a[54] | 2.5 | 1.5 | Netherland | Jan 2005-Dec 2009 | 111 | Average age 70.77 | M(n= 59/111) F(n= 52/111) | Any type | Terminally stage | General Practitioner Research Network | General Practitioner | 11.7% (n=13/111) | NR |
| Ng et al, 2014[55] | 2.5 | 2.5 | Malaysia | Jan 2008-Dec 2012 | 3345 | Average age 57 | M(n=1036/3345) F(n=2309/3345) | Any type | NR | Inpatient | NR | 7.8% (n=260/3345) | NR |
| Pearson et al., 2013[56] | 3.5 | 0.5 | Australia | Jan 2005-Dec 2009 | 5795 | Median age 82 | M(n=3660/5795) F(n=2135/5795) | Any type | NR | Veterans' population | General Practitioner | 17.2% (n=995/5795) | Type: SSRI-46.9%(n=469/995), TCA-32.9%(n=327/995) Other-20.2%(n=201/995) |
| Suppli et al., 2011[57] | 3 | 1.5 | Denmark | 1998-2006 | 4150 | NR | F(n=4150) | Breast(n=4150) | NR | Breast Cancer Cooperative Group | NR | 25% (n= 1020/4150) | NR |
| **Antidepressants prescription data reported from medical record/ chart & cancer registry** | | | | | | | | | | | | | |
| Wilson et al., 2007[58] | 2.5 | 1.5 | Canada | NR | 381 | Average age 67.2 | NR | Any type | Terminal stage | Inpatient, Palliative care units, Outpatient, Home care | NR | 22.5% (n=86/381) | Type: SSRI, TCA |
| **Antidepressants prescription data reported from health care professionals reporting questionnaire** | | | | | | | | | | | | | |
| Fisch et al., 2014[59] | 2.5 | 1.5 | USA | March 2006- May 2008 | 3106 | Average age 61 | M(n= 936/3106) F(n= 2170/3106) | Breast(n=1544), Colon(n=717), Lung(n=320), Prostate(n=525) | Any stage | Outpatient | NR | 19.3% (n=599/3106) | Type: SSRI/SNRIs,TCA, |
| **Antidepressants prescription data reported from self-reporting questionnaire/ interview** | | | | | | | | | | | | | |
| Brinkman et al., | 3 | 2 | USA | 1994-2007 | 8277 | NR | NR | Any type | NR | Childhood Cancer | Physician | 19.1% | NR |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2013[60] | | | | | | | | | | Survivor | | (n= 1527/8277) | |
| Lloyd-Williams et al., 2013[61] | 3 | 2 | UK | Nov 2007-Aug 2009 | 629 | Average age 66 | M(n=207/629) F(n=422/629) | Any type | Advanced cancer | Hospice day care units | NR | 25% (n=156/629) | Type: SSRI-70%, NSSA-30% Number: Recommended therapeutic dose ranges |
| Pasquini et al., 2006[62] | 2 | 2.5 | Italy | Oct 2003-July 2004 | 165 | Average age 58.2 | M(n= 73/165) F(n= 92/165) | Any type | Any stage | Hospital Patient | Psychiatrist | 20.6% (n=34/165) | Type: Mirtazapine (n=15/34)-15mg, Citalopram (n=13/34)-10mg, Escitalopram (n=4/34)-5mg, Fluvoxamine & Paroxetine-(n=2/34) |

[1]ranged from high quality (4) to low quality (1). [2]ranged from high risk (4) to no risk (0). SSRI- Selective serotonin reuptake inhibitor, TCA- Tricyclic antidepressant, MAO- Monoamine oxidase, SNRI- Serotonin–norepinephrine reuptake inhibitor, NSSA- Noradrenaline-serotonin specific antidepressant, NR- Not Reported

According to the World Psychiatric Association, the initial dose of an antidepressant should be about half of the expected therapeutic dose, with increased dosing depending on the changes in the depressive status of the patient (Riba and Grassi, 2008). Only Chaturvedi *et al*. (1994) and Pasquini *et al*. (2006) reported the dose of antidepressants, with Chaturvedi *et al*. (1994) highlighting the wide range of dose prescribed. Lloyd-Williams et al., (2013) indicated that patients were prescribed antidepressants according to recommended therapeutic dose ranges, but did not report the specific dose for each patient.

No clear pattern emerged when studies were grouped by time since diagnosis or time to death, with studies that focussed on the same time window reporting high or low rates, indicating that other variables such as type of study or type of data collection method may be more important to explain differences between studies. Only two studies focussed on antidepressant initiation before cancer diagnosis or treatment (Kelly et al., 2010 & Pearson et al., 2013). Among breast cancer patients, 44% of antidepressants (n=3,311/7,483) were prescribed concomitantly with Tamoxifen therapy, with the remaining patients prescribed antidepressants six months before starting breast cancer treatment (Kelly et al., 2010 ). From dispensing records Pearson *et al.* (2015) identified that 34.9% of patients (n= 347/995) were prescribed antidepressants three to four months before the cancer diagnosis. Early symptoms of cancer or prevention of depression when facing the diagnosis may explain this increase in prescriptions (Pearson et al., 2015). Another noticeable peak in antidepressant use was identified by three studies during the last three months of life (Ng et al., 2013b; Brelin et al. 2013 & Lloyd-Williams et al., 1999).

To achieve therapeutic action, antidepressants should be used for no less than eight weeks and continued for at least 24-36 weeks (Riba and Grassi, 2008; Lu and Roughead, 2012 & Shultz and Malone, 2013). In contrast, Lloyd-Williams and colleagues (2013) noted that the median duration of use was only 9.5 weeks. Pearson *et al*. (2015) identified a median duration of antidepressant use of 16 weeks with breaks and 11 weeks without breaks from the dispensed prescriptions. Furthermore, half of the patients (50.5%, n=502/995) discontinued treatment during the follow-up period (Pearson et al., 2013). However, Kelly *et al*. (2010) identified a long duration of use in breast cancer patients, with a median of 74.8 weeks.

Only two studies detailed the proportion of prescriptions by different medical specialties. In Cullivan *et al*. (1998) study (n= 16/63), oncologists were the most common prescriber (46%). Brelin *et al*. (2013) nationwide Norwegian research (n= 3,836/17,753) identified general

practitioners as the highest antidepressant prescribers (50%), with a very small proportion of prescriptions by oncologists (3.7%) or psychiatrists (0.8%) (Table 2.3).

### *2.3.3 Additional Analyses*

Overall, the studies showed significant heterogeneity (Q= 11464.11, $I^2$= 99·65%). The funnel plot showed asymmetry (Figure 3.1), indicating likely publication bias. Sensitivity analyses (Supplementary Table 2.1) eliminated studies with the highest and lowest prevalence of antidepressant prescriptions one by one, and grouped studies differently by decades (Supplementary Table 2.2), trends of prescription of antidepressants over time (Supplementary Table 2.4) and study period (Supplementary Table 2.5). None of these substantially changed the results or conclusions.

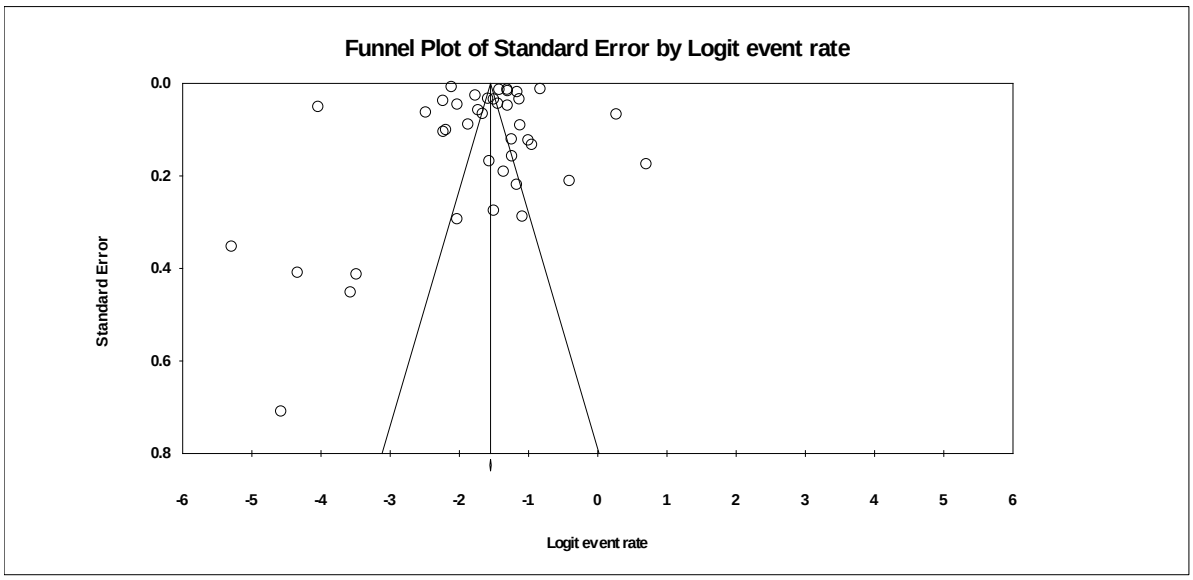


***Figure 2.3: Begg's funnel plot of standard error against logit event rate.***

## 2.4 Conclusions

According to the pooled estimate from all included studies, 15.6% of cancer survivors were prescribed antidepressants, which is higher compared to previous reports from the general population in the USA (11%) (Pratt et al., 2011). A large proportion of studies in our review (n=14/38, 37%) were conducted in the USA, and compared to these studies, antidepressant prescriptions were considerably less common in studies conducted in Asia (7.3%). Four case-control studies reported that a higher proportion of cancer patients were prescribed

antidepressants than non-cancer patients, if the data were collected from prescription or health records (Desplenter et. al., 2012; Ng et al, 2013b; Braun et al., 2015 & Jones et al., 2015). However, several studies identified a considerable treatment gap and potential under-use of antidepressants. For example, the rate of antidepressants users was much lower than the rate of cancer patients identified with depressive disorder using validated diagnostic depression scales (Cullivan et al., 1998; Desplenter et.al., 2012; Yokoyama et al., 2012; Fisch et al., 2014; Walker et al., 2014; Yokoyama et al., 2012 & Zhao et al., 2014). Even some cancer patients diagnosed with major depression were not receiving treatment for depression or support by qualified mental health professionals (Yokoyama et al., 2012 & Zhao et al., 2014). However, Mitchell *et al*. (2011) reported a pooled prevalence rate of depression of 16.5% (95% CI= 13.1-20.3) in patients from palliative care and advanced cancer care settings and if these patients were prescribed antidepressants this would reflect closely the rate of prescribing identified in this review.

Marked variation in prevalence rates were observed in this review including by study sample size, setting, data collection methods and time since diagnosis reflected in the sub-group results (Table 2.2, Table 2.3 and Figure 2.2). The sample size of the studies ranged from 63 to 113,887. Studies collected the data from different settings nationally (n=37) and multi-nationally (n=1) with different gender, population, community, and hospital inpatients or outpatients service characteristics. There was also a large difference in the duration of time for which prescription data was collected from a minimum of six months (Derogatis et al., 1979; Cullivan et al., 1998; Yokoyama et al., 2012 & Zhao et al., 2014) to a maximum of 12 years (Kelly et al., 2010 & de Bock et al., 2012). Several differences in prevalence rate of greater than 5% were observed in the sub-group analysis with place of study, decade of study and data sources all showing considerable variability (Table 2.2).

Pooled estimates of prevalence may not represent individual countries. To minimise this problem, we undertook sub-group analysis by continent (Table 2.2), which showed considerable discrepancy in prescribing especially for Asia with 4 out of 5 studies reporting lower prevalence rates than in studies (Yokoyama et al., 2012; Chien et al., 2013; Ng et al, 2014 & Zhao et al., 2014). Only Hung *et al*. (2013) identified a higher prevalence rate of antidepressant use and diagnosed mood disorder (19.6%, n=5,223/26,629) determined by International Classification of Diseases, 9th revision (ICD-9), in a nationwide population-based breast cancer study in Taiwan. Zhao *et al*. (2014) discussed potential reasons for low

rates of prescription of antidepressants in China. Unavailability of mental health professionals or psycho-oncology services in general hospitals was stated as a driving reason for both the high prevalence and low recognition of depression (any depressive disorder, 25.9%, n=119/460; recognised depression, 3.4%, n=4/119; prescribed antidepressants, 2.5%, n=3/119). Other problems included difficulties in diagnosis of depression, and inadequate training in recognising psychiatric symptoms (Zhao et al., 2014). Failure to diagnose depression and attention focussed on cancer treatments were also discussed as reasons for low prevalence of antidepressant use in Malaysia (7.8%, n=260/3,345) (Ng et al., 2014). Recognition of depression is challenging for non-mental health professionals (Couper et al., 2012). Zhong *et al*. (2010) conducted a study on recognition of depression in hospital inpatients in China and found that while 16.2% (n=83/513) and 9.4% (n=48/513) of patients had depressive and major depressive disorder according to DSM-IV, respectively, none of these patients had been recognised by health care professionals or received treatment. Low recognition of depression by prescribers has also been identified as a common problem among the general population in eight Asian countries (Chen et al, 2013) and European countries (Sharpe et al., 2004). Biological differences among Asians in their P450 cytochome enzymes in the liver, utilised in metabolism of antidepressants, may also explain lower utilisation rates in this ethnic group (van der Weide and Hinrichs, 2006).

Health care professional-reported data resulted in lower prevalence rates (10.9%) compared to other data collection methods (Fisch et al., 2014 & Janberidze et al., 2014). This may either reflect a more precise estimate or lack of awareness among the health care professionals that the patient is taking antidepressants from another prescriber. Pérez-Stable et al. (1990) conducted a study on physician-recognised depression (defined by a prescription of antidepressants) compared with Diagnostic Interview Schedule (DIS). Among 70 patients diagnosed with depression using the DIS, only 25 patients were identified by physicians. Two decades later Punekar et al. (2012) showed that use of antidepressants prescriptions had increased greatly in cancer patients, but underdiagnoses and underuse of effective treatments are still persisting in many countries around the world as discussed above.

Most of the studies (n=31) included patients diagnosed with multiple types of cancer, and considered which patients were more likely to be prescribed antidepressants depending on the origin of cancer, physical or socio-economic status (Table 2.2). Female cancer survivors diagnosed with breast cancer were more likely to be prescribed antidepressants compared to

other cancer survivors, for example those with colon, lung or prostate cancer (Ashbury et al., 2003; Khan et al., 2010 & Zhao et al., 2014). Women were three times more likely to have an antidepressant prescription compared to men (Male; 3%-8.5% vs Female; 9.2%-22.8%) of the same age range in one study (Pratt et al., 2011), consistent with higher rates of depression in women compared to men (Silva et al., 2014). Hormonal, psychosocial or disease factors are discussed as the possible reasons for high prevalence of antidepressant prescription (Kelly et al., 2010 & Suppli et al., 2011). Most of the studies indicated the reason for prescription of antidepressant was depression. Only few studies reported that the medication was prescribed for pain, anxiety (Coyne et al., 2004 & Brinkman et al., 2013), hot flushes, nerve pain, as psychostimulants (Fisch et al., 2015), for sleep (Jaeger et al., 1985), or somatization (Brinkman et al., 2013).

Few of the reviewed studies (n=6) reported details on the prescriber characteristics, and few (n=8) focussed on the exact details of the prescription. In part this may be associated with the data extraction methods, which also varied widely across the studies, and had a clear influence on the prevalence rate (Table 2.2). Prospective studies in oncology which assess in detail the reasons for prescribing of antidepressants from progress notes or indication present in the prescription record of hospital. The health care providers involved are urgently needed, as well as better data about the follow-up regimen used to assess the response to treatment, and potential side effects. During the quality assessment we identified that few studies reported the characteristics of the underlying population, therefore selection bias is a risk of most included studies, which could be addressed in future prospective studies.

Strengths of this study include its systematic search strategy, review of cross-sectional, cohort and case-control studies across five decades. It found a number of characteristics associated with prescribing, including continent, data source, patient gender, age and cancer type. It identified considerable heterogeneity and asymmetry in results, clearly highlighting that further high quality studies are required. Future studies may consider using more than one data source (for example extraction from clinical files complemented by patient self-report) and also report details that allow with certainty distinguishing whether the antidepressant medication was used to treat mental or physical symptoms. Few studies reported on who prescribed the medication. Those that did seem to indicate that prescriptions for antidepressants are rarely provided by mental health professionals, much more commonly by primary health care providers or non-psychiatrist physicians and it would be interesting to investigate if this makes a difference with regards to treatment adherence and follow-up.

Interactions between antidepressants and cancer treatment drugs are an increasing concern, and high quality data would allow to better discern which patients may be at risk of receiving suboptimal combinations of mental health and cancer fighting drugs.

### 2.5 Summary

This systematic literature review was undertaken as a part of Masters course and it was found that only one retrospective cohort study was conducted on this area in Australia. Different approaches were taken for the next research in this Masters research to assess the prescription practices of antidepressants to cancer patients in Australia. The potential research methods that could be employed and were considered included prospective cohort study, case-control study, or intervention study on different types of cancer patients or the major types of cancer such as lung, prostate, breast or blood cancer.

Additional factors that had to be taken into account in finalising the decision for the study design were optimal research method given the limited time frame available until completion of the course, data collection from newly recruited sample or exiting medical records, number of ethics application required to apply and other clearances, design and content of research, sample size, data analysis, cost of research and so on. After considering all these factors involved in the research, data collection from the existing medical records of a tertiary hospital that has a collaborative agreement with QUT was chosen the best way forward for this research in the limited time frame of Master course. The matched case-control study design showed the following merits -

- Allowed greater precision in estimates at comparatively small sample size
- Allowed to select the sample from a large comprehensive database system without direct patient involvement
- Conducted within the time frame of Master course
- Reasonably time-consuming ethics applications and other clearances
- No funding required

# Chapter 3: A retrospective case-control study

After the systematic literature review and meta-analysis was completed and all relevant approvals were obtained, data collection for the case-control study was conducted at a tertiary hospital in Queensland. While a cohort study design would have been ideal to prospectively assess the characteristics of newly diagnosed patients who are prescribed an antidepressant, this study design was too time consuming for data collection and too expensive for this Master's thesis. A cross-sectional study with direct involvement of the patients could have offered insight into the self-reported reasons for the prescription of the antidepressants, but was not taken consideration for master research because it was uncertain whether we could collect the number of sample at the limited time frame. Therefore considering all the possible options in research design and method, a retrospective matched case-control study was selected and offered the following advantages: abstractions of existing data from medical records without direct patient involvement; reasonable time required for ethics application and other clearances, no funding required in this project.

From the systematic literature review, different data collection methods were identified including prescription record, dispensing record, medical chart or cancer registry, patient self-reporting or health care professional reporting questionnaire. Dispensing record was the primary antidepressant data collection source from the hospital. However, data collection from the dispensing record of study characteristics in the study one, the pooled estimate of prevalence of antidepressants was low compared to other methods or overall pooled estimate. Additionally, it was unclear that patients took antidepressants regularly. To consider this limitation of this data collection method from dispensing record and to get current antidepressants prescription characteristics to cancer and non-cancer patients, we match the antidepressants dispensing record to the prescription record of inpatients from medical record of hospital.

### 3.1 Introduction

Cancer (16%) is the largest contributors to the burden of disease in Australia (AIHW, 2014). Co-occurrence with severe depression may lead to poorer outcomes and reduced survival (Hert et al., 2011). A large cohort study on adults (n= 89,574) in Australia 2006 to 2008 showed that approximate 6.7% of cancer patients (n= 26,382) were suffering from high levels

of psychological disorder compared to 7.8% of non-cancer subjects (Banks et al., 2010). The incidence of depression is higher (9.8%, n= 713/7298) in first year of diagnosis of cancer than in non-cancer patients (0.8%, n= 112/14596) (Desplenter et al., 2012).

Antidepressants are widely prescribed for the pharmacological treatment of depression and studies report that worldwide antidepressant prescribing has increased over the last three decades (Helgason et al., 2004, Moore et al., 2009, Pratt et al., 2011, Stephenson et al., 2012 & Kantor et al., 2015). Antidepressants improve depressive symptoms; however, they also have adverse effects and can interact with cancer and non-cancer medications (Chan et al, 2012; Gøtzsche, 2014; Yap et al., 2011). Various health professionals including physicians, oncologists, or psychiatrists have been identified as commonly prescribing antidepressants to cancer patients (Brelin et al., 2013). According to the Australian Institute of Health and Welfare on a population level, physicians prescribe 86% of antidepressants for the treatment of mental health in general, whereas psychiatrists prescribe only 8% and non-psychiatrists 6% of prescription medicines (AIHW, 2012). There is also variation in doses of antidepressants by provider to the depressive patients. Usually it has been identified that psychiatrists prescribe higher doses of antidepressants to the patients compared to general practitioners in Australia (McManus et al., 2003).

As described in chapter 2 a systematic literature search has been conducted and four case-control studies reported that the prevalence of antidepressants to cancer patients is higher than non-cancer or patients with chronic disease conditions (Desplenter et. al., 2012; Jones et al., 2015; Ng et al, 2013b & Braun et al., 2015). The prevalence rate ranged from 9.8% to 22.6%, with one study conducted on a large population-based cohort (Ng et al., 2013). None of the studies reported, however, what type or dose of antidepressants was prescribed to the cancer patients, which group of health care professionals prescribed most frequently to cancer patient comorbid with depression, whether the follow-up is similar to what is recommended for mental health symptoms in people without cancer, or reported on the adverse effect or drug-drug interaction of antidepressants.

### 3.2 Aims of the study

From the systematic review and meta-analysis and research gap, the following research aims have been identified:-

Objective one: To describe the sociodemographic and clinical characteristics of cancer inpatients and non-cancer inpatients prescribed with antidepressants;

Objective two: To compare the prescription profile of antidepressants in age and gender matched cancer and non-cancer inpatients;

Objective three: To determine the occurrence of adverse effects or potential drug-drug interactions of antidepressants with other prescribed medicines prescribed to cancer patients.

## 3.3 Research method

### *3.3.1 Research design*

A retrospective age and sex matched cohorts of cancer and non-cancer patients were identified to determine nature of antidepressants use in these two groups. Socio-demographic, clinical and medicine records of cancer and non-cancer patients were abstracted from the hospital database system.

### *3.3.2 Study setting*

This study was conducted at the Royal Brisbane & Women's Hospital (RBWH) which is a tertiary referral hospital in Queensland, the largest provider of health care services, and one of the busiest mental health services in Queensland (Queensland Health, 2013). Data were collected from the electronic records of the Department of Pharmacy, RBWH.

### *3.3.3 Study sample*

The inclusion and exclusion criteria for cases and control are described in table 3.1-

***Table 3.1: Inclusion and exclusion criteria of inpatients with antidepressant prescriptions***

| | **Inclusion criteria** | **Exclusion criteria** |
|---|---|---|
| **Cancer Patients** | • Patients >18 years<br>• Any type of cancer diagnosed in the last ≤12 months | • Recurrence or progression of cancer<br>• Cancer diagnosed ≥12 months |
| **Non-cancer Patients** | • Patients >18 years<br>• Age (±3 years) and gender matched case | • Inpatient for the treatment of mental health problem<br>• Previously diagnosis of cancer |

### *3.3.4 Medications of interest*

The list of antidepressants was collected according to the Anatomical Therapeutic Chemical (ATC) classification code (ATC/DDD Index, 2016). The ATC categorised antidepressants (N06A) as: N06AA (Non-selective monoamine reuptake inhibitors), N06AB (Selective serotonin reuptake inhibitors), N06AF (Monoamine oxidase inhibitors, non-selective), N06AG (Monoamine oxidase A inhibitors) or N06AX (Other antidepressants). Generic names of the medications prescribed for patients receiving cancer treatment or treatment for other diseases were collected. Additionally the date of prescription of each medicine, dose, and dosage form was extracted. A list of ceased medication was also collected. The number of other medications prescribed during hospitalisation, including supplementary or over the counter medicines, was also extracted. The recommended dose of antidepressant was determined from the defined daily dose present in the ATC classification code.

### *3.3.5 Diagnosis of depression*

A diagnosis of depression was identified through a review of all information contained in the hospital medical record including correspondence letters from general practitioners or other health professionals, RBWH internal referral letters, patient progress reports, patient self-report forms, discharge report, diagnostic test of depression report, or health assessment records. It was also extracted whether depression was reported as a comorbidity or pre-admission medical history.

For many patients depression was formally assessed at admission using the Patient Health Questionnaire (PHQ-2) most commonly conducted by a nurse as part of the standardised patient risk assessment (Appendix B: Patient Health Questionnaire). If the total score of the PHQ-2 is ≥3 out of 6 or the nurse is concerned about the patient's mood, a referral of the patient to the medical team to consider psychology or psychiatry treatment will be arranged. It is also recommended to include information about the PHQ results in the discharge summary to general practitioner.

### *3.3.6 Other variables*

Socio-demographic variables

Age, sex (Male), country of birth (Australian, non-Australian), patient status (alive, deceased), insurance (yes, no), alcohol and smoking status (current, past user, never), marital

status (married, widow, de facto, divorced/ separated, never married), living status (family, other, alone), employment (yes, no), concession status (yes, no) were extracted for case and control patients and used as adjustment variables in data analysis where applicable.

Clinical variables

The date of diagnosis with cancer was determined from the referral letter by health care professional to the hospital or progress report by hospital practitioner. Other clinical variables including cancer status (type of cancer, type of cancer treatment), personal and family history of depression (yes, no), depression information (date of diagnosis, referral for counselling or psychotherapy, antidepressants prescriber information, antidepressants start date), comorbidities, other mental problem, pain assessment, mental health assessment (PHQ-2 test or other) and their follow-up, other mental health assessment test, allergic or adverse reaction to antidepressants or other medicines were considered for data collection. Comorbidities of disease were categorised according to the International Classification of Diseases (ICD) (WHO, 2015).

### *3.3.7 Indication of antidepressant*

Antidepressant prescribed in the treatment of depression or other mental problem was determined from the information of depression present as comorbidity or pre-medical history in any documents of hospital database system. Indication of antidepressant was categorised into three ways-

1. Depression- Depression recorded as comorbidity in any documents of database. Only depression or depression with other mental health problems also was considered in this category.

2. Other mental health problem- No information about depression, but recorded other mental health problem was considered in this category.

3. Not recorded- No information of depression or any mental health problem in any documents of database was considered as not recorded.

### *3.3.8 Ethical clearance and other approval*

The study was considered low and negligible risk (LNR) research by the Royal Brisbane Women's Hospital Human Research Ethics Committee (HREC) as there was no contact or involvement of patients during the data collection process in the hospital throughout the

whole study timeline. There was no involvement of children and the age of the participants was18 years or older. Two ethical clearances were obtained to conduct the data collection process of this pilot retrospective case-control study- 1) Royal Brisbane Women's Hospital (RBWH) and 2) Queensland University of Technology (QUT) ethics committees.

Low or Negligible Risk research application for Ethical Review (Reference number: HREC/15/QRBW/137) was submitted to the RBWH Human Research Ethics Committee (HREC) with the approval from the Department of Pharmacy, RBWH to undertake the research (Appendix C: RBWH-HREC approval letter). The ethics application approval number was EC00172. After getting approval from the RBWH-HREC, Human-Administrative Review application was submitted to the Queensland University of Technology human ethics research committee and got the approval to conduct the research at the RBWH (Appendix D: QUT-HREC approval email). The QUT approval number was 1500000417.

To access the identifiable data and health information held by Queensland Health, Public Health Act – Application was submitted after consultation with the data custodian of RBWH who approved the application (Appendix E: Public Health Act approval letter) to access read only database present in the Department of Pharmacy, RBWH. The approval number was RD005678.

A research data agreement was negotiated between QUT and Metro North Hospital and Health Service (Department of Pharmacy, Royal Brisbane and Women's Hospital). The Research Governance Office provided the approval for all the documents including RBWH HREC, Public Health Act application, protocol of the study, data collection tool, letter of support from the from Department of Pharmacy, RBWH and curriculum vitae of Principal Investigator (Appendix F: Research Governance Office approval letter).

### 3.4 Data collection

Data were collected from the integrated electronic Medical Record (ieMR) database in the Department of Pharmacy, RBWH. The sources of each data collection as extracted are listed in the following Table 3.2.

***Table 3.2: Sources of data from RBWH***

| Data feature | Source |
|---|---|
| **A. Sociodemographic status** | |
| Age, Sex, Patient status, Country of origin, Religion, Marital status | ieMR patient information cover page |
| Living status | Health risk assessment questionnaire,<br>Occupational therapy initial assessment,<br>Progress report, |
| Alcohol/Smoking status | Health risk assessment questionnaire |
| Employment, Concession, Insurance | Occupational therapy initial assessment,<br>Patient Election form-Administration,<br>Patient registration form |
| **B. Clinical record** | |
| Cancer information- date of diagnosis, type<br>Comorbidities | Correspondence letters from General Practitioner or other practitioner,<br>External hospital reference,<br>RBWH internal reference letter,<br>Progress report,<br>Discharge report of RBWH and external hospital |
| Allergic or adverse reaction | ieMR patient information page,<br>Health risk assessment questionnaire |
| Depression information- Type, History<br>Other mental health problem | Correspondence letters from General Practitioner or other practitioner,<br>Hospital internal reference letter,<br>Progress report,<br>Health risk assessment questionnaire |
| Patient Health Questionnaire (PHQ-2) | Health risk assessment questionnaire |
| **c. Medicines record** | |
| Antidepressants | Dispensing record complemented by prescription record,<br>Progress record,<br>Any correspondence letter from RBWH internal or external reference,<br>Medication Action Plan (MAP) |
| Other medicines | RBWH prescription record,<br>Progress record,<br>Any correspondence letter from RBWH internal or external reference<br>Medication Action Plan (MAP) |

### *3.4.1 Selection of sample*

Data were extracted from patients who had been admitted as inpatients to the cancer, general medical, surgical or haematological wards of RBWH. Admission had to occur in the hospital in the timeline of January 2014 to July 2015 for the treatment of cancer or post-treatment procedure. Control patients were inpatients at the hospital for the treatment of chronic disease or accidental injury.

Initially cancer and non-cancer patients were selected at random from those that had a record of antidepressants present in the dispensing record of the RBWH. Cancer cases were searched

according to the inclusion criteria of patient diagnosed with new cancer within the past 12 months and prescribed antidepressants. Prescription of antidepressants within 12 months of cancer diagnosis was confirmed from the earliest date of dispensing record or prescription record. Cancer cases were excluded if the patients had progressive disease or recurrence of cancer or were prescribed antidepressants 12 months or more after cancer diagnosis.

Control patients prescribed antidepressants were selected then by age and gender matching the cancer patients. Control patients were inpatients with any chronic disease condition from general and surgical ward. During the matching of age, controls were selected with the closest age to the cancer patients; the maximum age band was ±3 years.

### *3.4.2 Clinical record*

Extracted data including comorbidities, allergic or adverse drug reaction, depression record or other mental health problems, all collected from the correspondence letters from General Practitioner or other practitioner, external hospital reference, RBWH internal reference letter, progress report, RBWH discharge report (Table 3.2). Comorbidity or pre-medical history of depression was collected from the practitioner referral information present in the database.

### *3.4.3 Medicine record*

Antidepressants as well as other medications prescribed to the patients were collected from the prescription record of the ieMR database. The list of antidepressants was collected according to the ATC Classification System. Initial source of antidepressants profile was the dispensing record. Data from the dispensing record were compared with the prescription record and any other hospital documents present in the database. Additionally date of prescription of each medicine and their dose as well as dosage form including oral, intravenous, topical were extracted. A list of medications ceased in the hospital was also extracted. Over the counter (OTC) medicines and supplementary lists were also collected from the hospital prescription record and the number of these counted in the total number of medications list.

## 3.5 Data quality and management

### *3.5.1 Confidentiality and security*

Patients were not involved in person or contacted for this research. However, data were collected through the identifiable Medical Reference Number (MRN) from hospital to select cases and matched controls. Every person was assigned in the data collection materials with an individual unique but meaningless identification code, while no names or age or any potentially identifiable codes were extracted.

After collecting the data, materials were kept in a secure place of the Research office in the Department of Pharmacy, RBWH. The outcomes of the data collection efforts are presented in aggregated format only to ascertain privacy of the patients.

### *3.5.2 Data entry*

The ieMR is a read-only access electronic patient clinical and medicine records database. Initially extracted data were entered in the primary paper-based data collection form (Appendix G: Data collection form). Patient identification number, age and gender were inserted into the separate sheet to allow matching to age and gender based control participants. Primary de-identified data were entered into the spreadsheet for data store and analysis.

### *3.5.3 Data storage*

Dispensing record materials as well as information of patient age and gender match sheet was stored in a secured place of research office of Department of Pharmacy, RBWH. Primary de-identified data collection materials were stored in the secured place of Principal Supervisor office at QUT. De-identified electronic data were saved on the secured drive of the QUT university network.

## 3.6 Data analysis

Conditional logistic regression was used as the statistical analysis method for the retrospective, matched case-control study. Each case was paired with one age and gender matched control to efficiently determine association of categorical variables (Breslow & Day, 1980; Bruce et al., 2008 & Rose and van der Laan, 2009). This analysis method is superior to reduce the bias of sample selection (Rothman and Greenland, 1998). The limitations of using

conditional logistic regression are that it is difficult to generate conditional distribution of statistics for continuous variables. This limitation can be overcome by converting continuous variables into categorical variables. Another limitation is that conditional logistic regression results in wider confidence intervals compared to standard logistical regression (Heinze, 2006).

Statistical analysis was conducted by using the Statistical Package for the Social Science (SPSS), Version 23. Missing variables were denoted as 'not recorded' covariate. For each objective the following analysis were conducted-

*Objective One: To describe the sociodemographic and clinical characteristics of cancer inpatients and non-cancer inpatients prescribed with antidepressants*

Descriptive analyses (frequencies, percentage for categorical variables) were conducted to describe the distribution of each sociodemographic variable of cases and controls. Sociodemographic characteristics were compared through categorical variables by contrast between case and control using conditional logistic regression. Odds ratio (OR), 95% confidence interval (CI) and *p*-values were reported for each covariate. Matched cox regression of survival analysis was used to describe the data.

Frequencies, percentages and conditional logistic regressions were also used to describe the clinical characteristics (including type, number and treatment of cancer; type of comorbidity) of cases and control. The type, number and treatment of cancer were presented by frequencies and percentages.

*Objective Two: To compare the prescription profile of antidepressants in age and gender matched cancer and non-cancer inpatients*

Statistical significance and clinical importance were considered to determine the association between case and control of sample. Conditional logistic regression was used to analyse the association of the matched case-control sample. Statistical significance was determined by *p* value ($<0.05$). Frequency was used to describe the prescription profile of antidepressants of cancer and non-cancer patients. The profile of inpatients of cancer and non-cancer patients who were prescribed antidepressants was described by using covariate analysis (including antidepressants used, number and ceased of antidepressants, referral refer to medical team or general practitioner to consider psychology or psychiatry treatment, patient seen by psychologist and psychiatrist, suicidal ideation, number of comorbidities and medicines, pain,

depression test follow-up). A descriptive prescription profile of antidepressants was tabulated including type and dose of antidepressants, change of dose with the mental health status of case and control, and by whether the patient received the prescription due to depression, other mental problem and no mental problem.

*Objective Three: To determine the occurrence of adverse effect or potential drug-drug interaction of antidepressants with other prescribed medicines to cancer patients*

The occurrence of adverse events and the exact symptoms was determined from the information present in the hospital database (Table 3.2) or patient self-report (indicated name of antidepressants as well as symptoms). Concomitant use of antidepressants and other medications prescribed at the same date and their potential drug-drug interactions were identified from drug-drug interaction present in the Australian Medicines Handbook, even if no actual adverse events were noted in the hospital database (Australian Medicines Handbook, 2015).

**3.7 Result**

Sample selection and inclusion

507 records were screened, after screening for the inclusion criteria and matching requirements, only 75 cases and 75 controls remained for the final analyses. Reasons for exclusions are described below and shown in Figure 3.1.

The records of 226 cancer patients with antidepressants were selected from the dispensing record taking antidepressants (Figure 3.1). Of these records had to be excluded because the diagnosis of cancer had been obtained more than 12 months ago, repeat of sample, no matching control, not visiting in the hospital or outpatients or no clear information about cancer date of diagnosis.

The records of 281 non-cancer patients were selected from the dispensing record of antidepressants at the same period of time. 75 controls were able to be matched with a maximum ±3 year age and gender of the cancer sample, after non-matching controls, controls who also had a cancer diagnosis, or other exclusion criteria were applied.

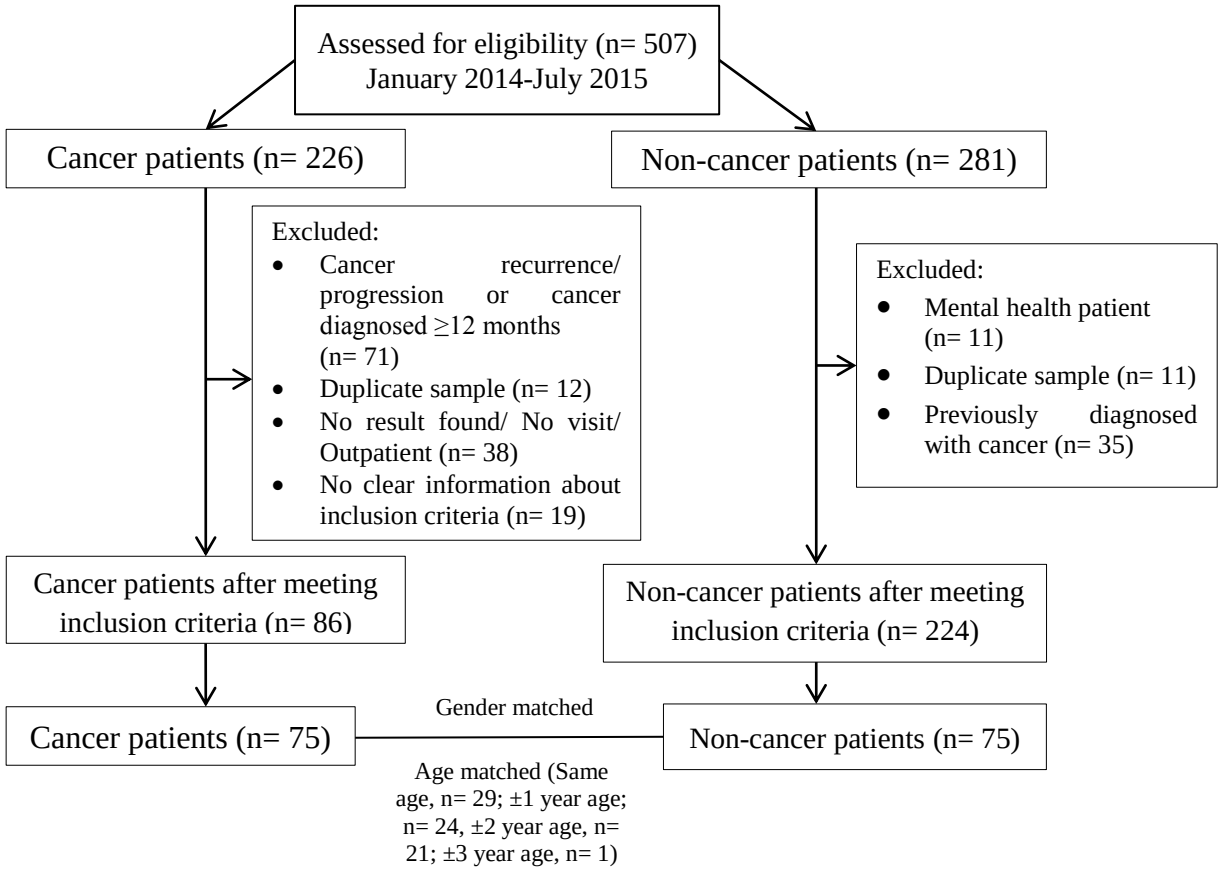


***Figure 3.1: Flow chart of sample selection and inclusion***

*Objective One: Compare the profile of inpatients of cancer and non-cancer inpatients who are prescribed antidepressants*

The comparison between cancer and non-cancer patients with antidepressants on socio-demographic and clinical characteristics is described in table 3.3.

The average age of both cancer and non-cancer patients was 60 years; around two-thirds were 65 years or older. About half of the sample were male (n=36, 48%). About one-third of the cancer sample (n= 24/75, 32%) was deceased within 18 months (whole time-line of the study) of cancer diagnosis, whereas only 5.4% of non-cancer patients died during the timeline of the study. This is reflected in the significantly greater odds of death in the cancer sample (n=24, 33% vs n=4, 5.4%; OR 65.29 (95% CI 1.79-2378.62); p= 0.02). Cancer patients (n=17, 22.7%) were more likely to have private insurance than non-cancer patients (n=11, 14.7%).

***Table 3.3: Socio-demographic & clinical status of cancer and non-cancer patients prescribed with antidepressants***

| **Characteristics** | **Cancer, n=75(%)** | **Non-cancer, n=75(%)** | **OR (95% CI)** | ***p* value** |
|---|---|---|---|---|
| Average age (range years) | $60_{(23-86)}$ | $60_{(22-88)}$ | | |
| Gender | | | | |
| Male | 36 (48.0) | 36 (48.0) | | |
| Patient status | | | | |
| Alive | 51 (68.0) | 71 (94.6) | - | - |
| *Deceased* | *24 (32.0)* | *4 (5.4)* | *65.29 (1.79-2378.62)* | *0.02* |
| Country of birth | | | | |
| Australia | 55 (73.3) | 61 (81.3) | - | - |
| Non Australian | 20 (26.7) | 14 (18.7) | 1.67 (0.73-3.81) | 0.22 |
| Private insurance | | | | |
| Yes | 17 (22.7) | 11 (14.7) | - | - |
| No/ Not recorded | 58 (77.3) | 64 (85.3) | 0.6 (0.26-1.37) | 0.26 |
| Alcohol status | | | | |
| Never | 30 (40.0) | 38 (50.7) | - | - |
| Current user | 35 (46.6) | 24 (32.0) | 1.96 (0.88-4.35) | 0.10 |
| Past user | 5 (6.7) | 8 (10.7) | 1.02 (0.28-3.71) | 0.97 |
| Not recorded | 5 (6.7) | 5 (6.6) | 1.23 (0.33-4.60) | 0.76 |
| Smoking status | | | | |
| Never | 27 (36.0) | 18 (24.0) | - | - |
| Current user | 21 (28.0) | 29 (38.7) | 0.45 (0.19-1.10) | 0.08 |
| Past user | 24 (32.0) | 22 (29.3) | 0.81 (0.34-1.94) | 0.64 |
| Not recorded | 3 (4.0) | 6 (8.0) | 0.37 (0.08-1.59) | 0.18 |
| Employment status | | | | |
| Yes | 24 (32.0) | 12 (16.0) | - | - |
| *No/Not recorded* | *51 (68.0)* | *63 (84.0)* | *0.37 (0.15-0.87)* | *0.02* |
| Age/Disability pensioner | | | | |
| Yes | 41 (54.7) | 52 (69.3) | - | - |
| *No/Not recorded* | *34 (45.3)* | *23 (30.7)* | *2.2 (1.01-4.88)* | *0.05* |
| Marital status | | | | |
| Married | 32 (42.7) | 15 (20.0) | - | - |
| Widow | 7 (9.3) | 7 (9.3) | 0.49 (0.13-1.89) | 0.30 |
| De facto | 3 (4.0) | 3 (4.0) | 0.58 (0.07-4.75) | 0.61 |
| Divorced/ Separated | 22 (29.4) | 21 (28.0) | 0.53 (0.21-1.35) | 0.19 |
| *Never married* | *10 (13.3)* | *26 (34.7)* | *0.20 (0.17-0.56)* | *0.002* |
| Not stated | 1 (1.3) | 3 (4.0) | - | - |
| *Living status* | | | | |
| *Family* | *43 (57.3)* | *22 (29.3)* | - | - |
| *Alone* | *21 (28.0)* | *25 (33.3)* | *0.37 (0.16-0.90)* | *0.03* |
| *Other*[1] | *7 (9.3)* | *19 (25.4)* | *0.16 (0.05-0.50)* | *0.002* |
| *Not recorded* | *4 (5.4)* | *9 (12.0)* | *0.23 (0.06-0.86)* | *0.03* |

Abbreviations: CI= Confidence Interval; OR=Odds Ratio. [1]Indicated living at shared place, community home, aged care, retirement village, nursing home or homeless. No statistics reported as age, gender were used for matching. Italicized entries indicate significant results.

There was no significant difference between cases and controls in current alcohol use-socially or regularly. More than half of the non-cancer patients (n=38/75) were never drinking alcohol, whereas the percentage was somewhat smaller in cancer patients (n=30, 40%). Overall, 60% (n= 45/75) of cancer patients were current or past smokers and about one-third of them (n= 18) were diagnosed with cancer of the respiratory tract and oral cavity

and 5 patients were diagnosed with lung cancer. Conversely, more than two-third of non-cancer patients (n=51, 68%) were current or past user of smoking.

About one-third of the cancer patients (n=24, 32%) were employed, compared to only 16% (n=12) for non-cancer patients. Other patients in both groups were unemployed (n=51, 68% vs n= 63, 84%; *p*= 0.02) or did not hold aged or disability concession (n= 34, 45.3% vs n= 23, 30.7%; *p*= 0.05). About 57.3% (n=43) of cancer patients were living with their family, whereas only 29.4% (n=22) of non-cancer patients were married and lived with family. Cancer patients were significantly less likely to have never been married compared to non-cancer patients (n=10, 13.3% vs n= 26, 34.7%; *p*= 0.002).

The clinical status of cancer and non-cancer patients is presented in table 3.4 and includes the information of cancer profile for cases and type of comorbidities for both groups. A quarter of the cancer patients were diagnosed with haematological cancer (n=19, 25.3%) and other cancer diagnoses were cerebral (n=9, 12%), breast, lung or face/oesophagus/tongue (n=8, 10.7% each) cancer. All cancer patients were receiving chemotherapy (n=24, 32%) or radiotherapy (n=22, 29.3%) or both (n=24, 32%).

A wide range of comorbid conditions were identified in the cancer and non-cancer patients (Table 3.4). The proportion of chronic diseases was consistent across the two groups including circulatory disease (n= 43, 57.3% vs n= 41, 54.7%; hypertension or arterial fibrillation), endocrine disorder (n= 31, 41.3% vs n= 28, 37.3%; diabetes mellitus, hypothyroidism), respiratory disease (n= 27, 36% vs n= 34, 45.3%; asthma), blood disorder (n= 20, 26.7% vs n= 24, 32%; hyperlipidaemia) or bone and joint disease(n= 15, 20% vs n= 20, 26.7%; arthritis) (Table 3.4).

***Table 3.4: Clinical status of cancer patients & non-cancer patients***

| | **Cancer, n=75(%)** | **Non-cancer, n=75(%)** | **OR (95% CI)** | ***p* value** |
|---|---|---|---|---|
| Cancer Type | | | | |
| Blood | 19 (25.3) | | | |
| Brain | 9 (12.0) | | | |
| Breast | 8 (10.7) | | | |
| Face/Oesophagus/Tongue | 8 (10.7) | | | |
| Lung | 8 (10.7) | | | |
| Gynaecological | 6 (8.0) | | | |
| Bowel & Colorectal | 5 (6.6) | | | |
| Oropharyngeal | 4 (5.3) | | | |
| Other | 8 (10.7) | | | |
| Number of cancer | | | | |
| Single cancer | 64 (85.3) | | | |
| More than one cancer | 11 (14.7) | | | |
| Cancer Treatment | | | | |
| Chemotherapy | 24 (32.0) | | | |
| Radiotherapy | 22 (29.3) | | | |
| Both | 29 (38.7) | | | |
| Circulatory diseases | | | | |
| Yes | 43 (57.3) | 41 (54.7) | - | |
| No | 27 (36.0) | 34 (45.3) | 0.83(0.42-1.65) | 0.60 |
| Not recorded[1] | 5 (6.7) | 0 | - | |
| Endocrine diseases | | | | |
| Yes | 31 (41.3) | 28 (37.3) | - | |
| No | 39 (52.0) | 47 (62.7) | 0.76(0.40-1.46) | 0.41 |
| Not recorded | 5 (6.7) | 0 | - | |
| Respiratory diseases | | | | |
| Yes | 27 (36.0) | 34 (45.3) | - | |
| No | 43 (57.3) | 41(54.7) | 1.31(0.68-2.51) | 0.41 |
| Not recorded | 5 (6.7) | 0 | - | |
| Digestive diseases | | | | |
| Yes | 24 (32.0) | 32 (42.7) | - | |
| No | 46 (61.3) | 43 (57.3) | 1.43(0.72-2.83) | 0.30 |
| Not recorded | 5 (6.7) | 0 | - | |
| Blood disorder | | | | |
| Yes | 20 (26.7) | 24 (32.0) | - | |
| No | 50 (66.6) | 56 (68.0) | 1.23(0.59-2.56) | 0.58 |
| Not recorded | 5 (6.7) | 0 | - | |
| Bone & joint disorder | | | | |
| Yes | 15 (20.0) | 20 (26.7) | - | |
| No | 55 (73.3) | 55 (73.3) | 1.25(0.58-2.68) | 0.56 |
| Not recorded | 5 (6.7) | 0 | - | |
| Nervous system diseases | | | | |
| Yes | 14 (18.7) | 21 (28.0) | - | |
| No | 56 (74.6) | 54 (72.0) | 1.33(0.56-3.16) | 0.51 |
| Not recorded | 5 (6.7) | 0 | - | |
| Renal system disease | | | | |
| Yes | 10 (13.3) | 12 (16.0) | - | |
| No | 60 (80.0) | 63 (84.0) | 1.25(0.49-3.17) | 0.64 |
| Not recorded | 5 (6.7) | 0 | - | |

Abbreviations: CI= Confidence Interval; OR=Odds Ratio[1]No information of any comorbidity in the database.

*Objective Two: Compare the prescription profile of antidepressants in age and gender matched cancer and non-cancer inpatients*

The comparative profile of cancer and non-cancer patients with regards to the profile of antidepressants is described in table 3.5. There were significant differences in the odds of being prescribed antidepressants for the treatment of depression (n= 50, 66.7% vs n= 59, 78.6%; *p*= 0.05) and other mental health problems (n= 8, 10.6% vs n= 11, 14.7%; *p*= 0.02) between the cancer and non-cancer patients. No information of any mental health problem was present in groups (n=17, 22.7% vs n=5, 6.7%). Antidepressant used in the treatment of depression and other mental problem was identified from the corresponding letter, progress report, and hospital internal reference letter or health risk assessment questionnaire (Table 3.2). Other mental problem was including anxiety, bipolar disorder (BPD), confusion & agitation, schizophrenia, chronic fatigue, personality or obsessive compulsive disorder.

Two-third of the cancer patients (n=50, 66.7%) were prescribed antidepressants for the treatment of depression denoted by health care professionals as a comorbidity or in the pre-admission medical history presented in the clinical record (Table 3.5). However, when we looked at the prescription record of antidepressant, other mental health problems were mentioned as reasons for prescription of antidepressants. Only 14% (n=7/50) of cancer patients were prescribed antidepressants for the treatment of depression mentioned in the prescription record filled-up by health care providers in hospital. Another 12% of cancer patients (n=6/50) were stated in the prescription record for other mental problem including anxiety, bipolar disorder (BPD) or side-effects of cancer treatment including problems with sleep, appetite, and pain.

A greater proportion of non-cancer patients (n=20/75, 26.7%) were prescribed two or more antidepressants compared to the cancer patients (n=15/75, 20.0%). Three cancer patients and one non-cancer patient had notes that they had ceased antidepressants. There was no significant difference between cancer and non-cancer patients regarding the proportion with a referral to the medical team for psychological or psychiatry treatment and a similar proportion of patients were already seen or consulted by a psychologist or psychiatrist or other mental health services in the hospital or community.

***Table 3.5: Profile of cancer and non-cancer inpatients prescribed antidepressants***

| **Profile of inpatients** | **Cancer, n=75(%)** | **Non-cancer, n=75(%)** | **OR(95% CI)** | ***p* value** |
|---|---|---|---|---|
| Indication for antidepressants[1] | | | | |
| Depression | *50 (66.7)* | *59 (78.6)* | - | - |
| Other mental health problem | 8 (10.6) | 11 (14.7) | 0.81 (0.30-2.17) | 0.67 |
| *Not recorded* | *17 (22.7)* | *5 (6.7)* | *4.56 (1.30-15.93)* | *0.02* |
| Number of antidepressant prescriptions in the medical record | | | | |
| One antidepressant | 60 (80.0) | 55 (73.3) | - | - |
| More than one antidepressant | 15 (20.0) | 20 (26.7) | 0.70 (0.34-1.48) | 0.35 |
| Ceased antidepressant[2] | | | | |
| Yes | 3 (4.0) | 1 (1.3) | - | - |
| No | 72 (96.0) | 74 (98.7) | 0.50 (0.04-5.51) | 0.57 |
| Referred to medical team or GP to consider psychology or psychiatry treatment | | | | |
| Yes | 13 (17.3) | 15 (20.0) | - | - |
| No | 62 (82.7) | 60 (80.0) | 1.20 (0.52-2.78) | 0.67 |
| Patient seen/consulted by psychologist or psychiatrist in hospital and community | | | | |
| Yes | 7 (9.3) | 10 (13.3) | - | - |
| No | 68 (92.7) | 65 (86.7) | 1.50 (0.53-4.21) | 0.44 |
| Patient under mental health services | | | | |
| Yes | 3 (4.0) | 8 (10.7) | - | - |
| No | 72 (96.0) | 67 (89.3) | 2.67 (0.71-10.05) | 0.15 |
| Suicidal ideation | | | | |
| Yes | 6 (8.0) | 16 (21.3) | - | - |
| *No* | *69 (92.0)* | *59 (78.7)* | *2.67 (1.04-6.81)* | *0.04* |
| Number of comorbidities | | | | |
| 1-2 | 23 (30.7) | 18 (24.0) | - | - |
| 3-4 | 28 (37.3) | 24 (32.0) | 0.90(0.38-2.14) | 0.81 |
| 5-6 | 16 (21.3) | 23 (30.7) | 0.56 (0.22-1.42) | 0.22 |
| *>7* | *3 (4.0)* | *10 (13.3)* | *0.17 (0.03-0.88)* | *0.03* |
| Not recorded[3] | 5 (6.7) | 0 | - | - |
| Total number of medicines and supplementaries prescribed during hospital stay | | | | |
| *0-10* | *6 (8.0)* | *14 (18.7)* | - | - |
| 11-20 | 26 (34.7) | 37 (49.3) | 1.58 (0.51-4.84) | 0.42 |
| *21-30* | *30 (40.0)* | *18 (24.0)* | *3.52 (1.11-11.21)* | *0.03* |
| *≥31* | *13 (17.3)* | *6 (8.0)* | *4.82 (1.10-21.11)* | *0.04* |
| Pain | | | | |
| Yes | 44 (58.7) | 37 (49.3) | - | - |
| No | 22 (29.3) | 31 (41.3) | 0.58 (0.28-1.21) | 0.15 |
| Not recorded | 9 (12.0) | 7 (9.3) | 1.22 (0.33-4.49) | 0.76 |
| *Depression test (PHQ-2) follow-up* | | | | |
| *Yes* | *32 (42.7)* | *17 (22.7)* | - | - |
| *No* | *29 (38.6)* | *39 (52.0)* | *0.39 (0.17-0.86)* | *0.02* |
| *Not recorded* | *14 (18.7)* | *19 (25.3)* | *0.33 (0.11-0.95)* | *0.04* |

Abbreviations: CI= Confidence Interval; OR=Odds Ratio. Italicized entries indicate significant results. [1]Based on comorbidity or pre- medical history of patients. [2]The sources of ceased antidepressant were patient self-report or referral from other hospital. [3]Excluded from the statistical analysis.

A significant number of patients reported suicidal ideation, but the proportion of cancer patients was lower than non-cancer patients (n=6, 8% vs n= 16, 21.3%). A notable result was identified with regards to the depression test (PHQ-2) follow-up, with significantly more cancer patients having such follow-up notes (n=32, 42.7% vs n=17, 22.7%).

Table 3.6 provides prescription characteristics of antidepressants to cancer and non-cancer patients. Supplementary table 2.6 shows the type and dosage information of prescribed antidepressants for each group. The total number of antidepressant prescriptions was 90 for cancer patients and 95 for non-cancer patients. Mirtazapine (n=11/50) was the most commonly prescribed antidepressants for the treatment of depression to cancer patients followed by duloxetine (n=9/50), and escitalopram (n=8/50). Non-cancer patients were most commonly prescribed desvenlafaxine (n=15/59), mirtazapine (n=11/59), or escitalopram (n=8/59) for the treatment of depression. Cancer patients identified as no mental health problem were also prescribed mirtazapine (n=6/17) more, followed by amitriptyline (n= 3/17), fluoxetine (n= 3/17), meclobemide (n= 2) was prescribed only to cancer patients and nortriptyline (n= 2) only to non-cancer patients (Supplementary table 2.6).

Variations of dose of antidepressant from the recommended therapeutic dose were identified in both case and control patients (Table 3.6). The recommended dose of antidepressants (n=24/59) was prescribed more to the cancer patients for the treatment of depression compared to non-cancer patients (n=29/75). Non-cancer patients (n= 34/75) who received antidepressants for depression were prescribed the medication at higher than recommended dose compared on 22 cancer patients. This could indicate that dose adjustments are less commonly conducted in cancer patients and needs to be investigated further in future research.

The number of antidepressants prescribed to a patient and change of dose during the whole study timeline was not significantly different in cancer and non-cancer patients. Only five non-cancer patients were prescribed with a changed antidepressant from the previous one compared to two cancer patients.

***Table 3.6: Prescription characteristics of antidepressants to cancer and non-cancer patients***

| | **Cancer** | | | **Non-cancer** | | |
|---|---|---|---|---|---|---|
| | **Depressive patient (n= 50)** | **Other mental health problem (n= 8)** | **No information of mental health problem (n= 17)** | **Depressive patient (n= 59)** | **Other mental health problem (n= 11)** | **No information of mental health problem (n= 5)** |
| Antidepressant prescription (n) | 59 | 10 | 21 | 75 | 13 | 7 |
| **Most commonly prescribed antidepressant** | Mirtazapine (n=11) | Mirtazapine (n=5) | Mirtazapine (n=6) | Desvenlafaxine (n=15) | Venlafaxine (n=3) | Mirtazapine (n=3) |
| **Variation of dose** | | | | | | |
| Lower dose | 13 | 4 | 5 | 12 | 3 | 3 |
| *Recommended dose* [1] | *24* | *6* | *9* | *29* | *4* | *2* |
| Higher dose | 22 | - | 7 | 34 | 6 | 2 |
| **Number of antidepressant** | | | | | | |
| 1 | 41 | 6 | 13 | 52 | 9 | 3 |
| ≥2 | 9 | 2 | 4 | 11 | 2 | 2 |
| **Change of dose** | 11 | - | - | 10 | 1 | 1 |
| **Change of antidepressant** | 1 | - | 1 | 5 | - | - |

[1]indicated type and dose of antidepressants according to Anatomical Therapeutic Chemical (ATC) Classification System. Italicized entries indicated the recommended dose.

*Objective Three: Occurrence of adverse effects or potential drug-drug interactions of antidepressants with other prescribed medicines to cancer patients*

Four cancer patients and three non-cancer patients experienced adverse events attributed to their antidepressants according to clinical record (Table 3.2). Only two cancer patients reported symptoms of adverse events including tongue swelling (Venlafaxine) and nausea (Escitalopram).

There were no specific notes by health care professionals identifying drug-drug interactions in the clinical or medicine record. However, a number of cancer patients were prescribed medications that were contra-indicated with their antidepressant due to the potential for drug-drug interaction between antidepressants and other prescribed medicines as listed in table 3.7.

About one-third of cancer patients (n= 23) and more than one-fourth non-cancer patients (n=18) had identified as potential drug-drug interaction with their prescribed antidepressant.

***Table 3.7: Probable drug-drug interactions in cancer patients***

| Antidepressant | Contra-indicated medication | Probable drug-drug interaction | Cancer (n=23)[1] | Non-cancer (n= 18)[1] |
|---|---|---|---|---|
| Amitriptyline | Fluoxetine | Fluoxetine inhibits hepatic metabolism of amitriptyline caused toxicity. | 2 | - |
| Fluoxetine | Warfarin | Risk of bleeding | 1 | 2 |
| Mirtazapine | Levodopa | Psychosis, suicidal ideation | 1 | 1 |
| SSRIs[2] | Heparin | Risk of bleeding | 7 | 4 |
| SSRIs[2] | Oxycodone | Risk of serotonin syndrome | 12 | 7 |
| SSRIs[2] | NSAIDs[3] | Risk of upper gastrointestinal bleeding | 3 | 5 |
| Venlafaxine | Heparin | Risk of bleeding | 2 | 1 |
| Venlafaxine | Amoxicillin-Clavulanic acid | Risk of serotonin syndrome | 1 | - |

[1]Patients may suffer from two or more drug-drug interactions. [2]Selective serotonin reuptake inhibitors (SSRIs). [3]Nonsteroidal anti-inflammatory drugs (NSAIDs)

## 3.8 Discussion

### *3.8.1 Overview*

The main findings of this case-control study include the significant differences between cases and controls with respect the indication of antidepressants as well as variation in type of antidepressants. There were also between group differences in a number of socio-demographic (patient status, suicidal ideation, employment or concession status) and clinical characteristics (comorbid chronic disease conditions), as might be expected.

More non-cancer patients were prescribed antidepressants for the treatment of depression, whereas mixed reasons for indication of antidepressants including anxiety, BPD as well as physical symptoms such as problems with sleep, appetite or pain were identified from the prescription records of cancer patients. The proportion of patients for whom no record of mental health problems was found in their clinical record was higher in cancer patients (n= 17, 22.7%) than non-cancer patients (n= 5, 6.7%) (Table 3.5). In considering the type of antidepressants, mirtazapine was prescribed more to cancer patients for the treatment of depression (n= 11) and unidentified reasons (n= 6) (Table 3.6). This is consistent with a previous study (Farriols et al., 2012) and likely due to mirtazapine being well-tolerated and

safe antidepressants for daily administration. Additionally it shows potential effect on pain besides depression (Freynhagen et al., 2006), and has a role in the treatment of chemotherapy-induced loss of appetite (Australian Medicines Handbook, 2015 & Griffin et al., 1996).

The proportion of patients who were unemployed or had concession status prescribed with antidepressants was high in both groups. This result is in line with a study conducted in Australia from 2003-2005 which showed that patients with low socio-economic status group more commonly utilise antidepressants compared to patients with higher socioeconomic status ($p<0.001$) (Page et al. 2009). Future longitudinal studies could seek to clarify this relationship and whether better access to behavioural therapy or supportive care could alleviate this inequitable use of antidepressants by socioeconomic status.

It must be of concern to health professionals that so many patients had suicidal ideation despite taking antidepressants. The proportion was higher in non-cancer patients (21.3%, n= 16), but still considerable among cancer patients (8%, n= 6). Choice of antidepressants prescribed by health care professional also varied between the groups. Desvenlafaxine is used for the treatment of major depressive disorder and this was more commonly prescribed to the non-cancer patients (Australian Medicines Handbook, 2015). Conversely, mirtazapine is well known for its benefits of appetite and sleep and was frequently prescribed to the cancer patients. However, these medicines are more commonly associated with patients' suicidal thoughts and behaviour (Australian Medicines Handbook, 2015). Future studies should investigate this further and assess whether additional psychotherapy may assist these patients to improve in their depressive symptoms (Sharpe et al., 2014).

Few previous studies investigated the association between comorbid diseases and antidepressants uses (Ashbury et al., 2003; Ng et al, 2013b & Jones at al., 2015). In our study, fewer cancer than non-cancer patients had more than seven chronic disease conditions. The majority of the sample experienced several comorbidities such as hypertension, diabetes, arthritis, GORD and these may affect the pharmacological treatment of depression. A review showed that patients with comorbidities including myocardial infarction, stroke, diabetes, cancer, and rheumatoid arthritis are less likely to respond to antidepressant treatment due to their comorbidities (Iosifescu et al., 2004). This needs to be taken into account when prescribing antidepressants to multimorbid patient populations such as those involved in this study.

This study found some evidence for drug-drug interactions of concern. A number of cancer patients (n= 23) could have potentially suffered one or more potential drug-drug interaction compared to 18 non-cancer patients, however, only seven patients actually had notes about adverse events occurring in their patient record. From the retrospective data it is not possible to discern whether because adverse events actually did not occur or may be underreporting of such events, and future prospective studies are needed to better clarify this question. Major drug interactions may occur between escitalopram and oxycodone and these medications were prescribed to two patients simultaneously. Twelve patients were prescribed with escitalopram and oxycodone which should not be used simultaneously due to risk of serotonin syndrome. A number of antidepressants are known to reduce the effectiveness of anticancer drugs including tamoxifen, doxorubicin, irinotecan, gefitinib, imatinib and so on (Chan et al., 2012). In this study none of the cancer patients were prescribed such combinations, but the proportion of cancer patients with each individual cancer was very small thus limiting the likelihood to detect such combined prescribing.

### *3.8.2 Strength of the study*

This study provided detailed prescription characteristics of antidepressants taken by cancer or non-cancer inpatients including type, dose, variation of dose from recommended therapeutic dose, probable drug-drug interactions. The case-control design identified factors that impact on the prescription practices for cancer patients, including reason for prescribing antidepressant, patient status, co-morbidities, and suicidal ideation. Approximately 33% (n=75/226) of cancer inpatients prescribed with antidepressants within 12 months of cancer diagnosis treated at the RBWH in the department of Pharmacy or between January 2014 and July 2015 were included in our study. This pilot retrospective case-control study thus provided a contemporary overview of prescription characteristics of antidepressants to cancer and non-cancer patients in Australia.

The case-control sample was chosen, as it is the most appropriate design for addressing the research aims-

- Identified a matched sample which allowed extracting differences in antidepressant prescribing pattern between cancer and non-cancer patients.
- Detailed prescription characteristic of antidepressants- type, dose, variation of dose from recommended therapeutic dose, probable drug-drug interactions.

- Included a large proportion of the available patients from two wards.
- Provided the groundwork for a future national larger study on medication practices in mental health for cancer patients.

### *3.8.3 Limitations of the study*

Our study has a number of limitations. We intended to comprehensively describe the prescription practices of antidepressants to cancer and non-cancer inpatients and whether these were provided for mental health or physical health reasons. The main limitation of this study was that many patients were referred from other hospitals to this tertiary centre, and medical as well as prescription information may have been reported elsewhere. However, for a considerable number of patients (n= 32), we could not identify a detailed report of reason for antidepressants prescription to the patients, or the starting date of antidepressants. It was also frequently not possible to identify the prescriber characteristics for antidepressant prescription including who first prescribed the antidepressant, or reasons for changing dose and type of antidepressant. The exact starting date of antidepressants could only be identified for five cancer patient from the database system. Due to under-reporting of starting date of antidepressants and prescriber characteristics, we could not identify whether patients took antidepressants before or after diagnosis of cancer, the detailed reason for prescription of antidepressants or whether suicidal ideation occurred before or after the prescription of antidepressants.

In some instance, there could be overlap of indication of antidepressants for the treatment of depression and other mental health condition or physical side effect. We could identify indication of antidepressant from prescription recorded by health care professionals only from 12% (n=13/90) of cancer and 2% (n= 2/95) of non-cancer inpatients. This limitation could be resolved in a future prospective study by regularly conducting a diagnostic test to determine depression of the study; however, in the current study diagnostics tests to determine depression were rarely recorded in the hospital database system. Several other results of this study also require confirmation in future prospective data collection; for example, whether adverse events occur if medications are given simultaneously despite such combinations not recommended, or whether patients improve in their depressive symptoms despite lower than recommended dose of antidepressants.

Lack of documentation about regular follow-up or social support as well as information about family history of depression were also identified from the database system. The corresponding letter from the health care professionals referring the patients to the hospital mainly reported the cancer related information. The PHQ-2 was conducted frequently, but not always during patients' hospital admission for cancer treatment, but often was not repeated limiting the assessment whether the antidepressants led to a reduction in symptomatology.

# Chapter 4: Recommendations and conclusions

## 4.1 Public health significance

Study one provided a thorough literature review at international level. This will allow researchers as well as health care professionals, not only from Australia, but also from other countries to obtain a succinct overview of prescription practices of antidepressants over more than four decades. The meta-analysis showed a pooled estimate of prescription prevalence of antidepressants to cancer patients of 15.6% (95%CI= 13.3%-18.3%). Through its subgroup analysis by study and patient characteristics, the result also shows that prescriptions of antidepressants were more common in female (22.6%; 95% CI= 16.0-31.0) or breast cancer patients (n= 6/7, 22.6%; 95% CI= 16.0-30.9). It also found a greatly reduced frequency of prescribing in Asian countries. Data from Australia was limited with only one eligible study identified. These findings indicate the importance of further public health research to better understand differentials in prescribing and follow-up through future in-depth studies in Australia. The lack of detailed data in the literature especially on the exact dose or length of time antidepressants were prescribed to cancer patients also indicated the presence of significant knowledge gaps that need to be addressed in future work.

Study two was conducted at one major hospital. It has delivered a significant contribution to the public health in Queensland as well as Australia by describing in detail the prescription practices of antidepressants to cancer and non-cancer patients. The results of this study have provided the major features associated with the mental health treatment of cancer patients for health care professionals. Key findings include an overview of prescription practices of antidepressants and potential risks of prescription to cancer patients. This study also describes prescription characteristics of antidepressants including type, variation of dose, and number antidepressants prescribed which is important for the health care professionals regarding the current practice of antidepressants. Moreover, study findings also indicate the importance of follow-up of mental health and pharmacological treatment, awareness of the prescription status of newly diagnosed cancer patients and that their prescription is suitably adjusted to address changes in mental health wellbeing.

### 4.2 Future research

The combined results of study 1 and 2 indicate that the prescription practices of antidepressants for the treatment of depression in cancer patients in Australia is under-researched and prospective cohort studies are required in the future to address the following research gaps:

- Besides the data collected in the present case-control study (Appendix G: Data collection form), it would be beneficial to also determine other factors including knowledge about the benefits of taking antidepressants of cancer patients, medication adherence, impact on their quality of life, relevance and changes in clinical depression tests such as the PHQ and follow-up by survey or patient self-reported questionnaire.
- The prevalence of antidepressants or other medicines prescribed for the treatment of depression to cancer patients diagnosed with common type of cancer- breast, lung, prostate or bowel needs to be studied in greater detail to determine how well this treatment is used for mental health issues and whether it is effective.
- It is also necessary to determine the mental health status of long-term cancer survivors and their antidepressants prescription treatment pattern.
- Due to identifying a high prescription prevalence of antidepressants to breast cancer or females in the meta-analysis, more research in women diagnosed with gynaecological cancer is also essential in Australia to identify the impact of cancer diagnosis on females and treatment of mental health in these patients.
- Besides the potential of adverse effects and drug-drug interactions of antidepressant with anticancer treatments, some researchers have raised concern that antidepressants may cause development of cancer or increase the mortality from cancer (Nordenberg et al., 1999). Research in this area has been conducted widely in other countries (Cotterchio et al., 2000; Ashbury et al., 2010; Cronin-Fenton et al., 2011; Walker et al., 2011) and should be considered for future research projects in Australia too.
- Review of prescription characteristics of antidepressants that are used for the treatment of mental health issues other than depression to cancer patients could identify if these medications have the desired effect and whether they are being ceased when the symptom burden is reduced.

### 4.3 Conclusions

In conclusions, antidepressants are commonly prescribed in the treatment of depression and other unidentified problems in cancer patients. It may be of concern that the reason for a significant proportion of antidepressant prescriptions to cancer patients could not be identified from the clinical or prescription records, especially given their potential for adverse effects and drug-drug interaction with other medicines. With better treatments and earlier detection the survival rate of cancer patient has increased significantly over the past decades; however, comorbidity of depression threatens the quality of life of cancer patients.

Prospective cohort studies may be the next logical step to determine the current knowledge gaps and limitations identified from the systematic literature search and retrospective study conducted for this thesis. Attention needs to be taken for the correct prescription practices of antidepressants. Prospective studies may also be useful not only to thoroughly assess the present status of mental health of cancer patients but also to show the value of regular follow-up of depression status after prescribing antidepressants. Patient self-administered questionnaires may be a suitable data collection method to ascertain not only the patients' wellbeing but also prescriber characteristics and may also overcome missing data identified from the present research method.

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# Appendix A: Supplementary Tables

### Supplementary Table 2.1: Sensitivity Analysis

| Name of study | Prevalence of antidepressant and total number of sample | Pooled estimate after sensitivity analysis | Weight (%) |
|---|---|---|---|
| Chaturvedi et al., 1994[37] | 67% (n= 146) | 14.8% (95% CI; 12.5%-17.3%) | 2.51% |
| Findley et al., 2012[40] | 57.7% (n=865) | 14.9% (95% CI; 12.6%-17.4%) | 2.69% |
| Derogatis et al., 1979[31] | 0.5% (n=1,579) | 16.5% (95% CI; 14%-19.4%) | 2.01% |
| Yokoyama et al., 2012[42] | 1% (n=194) | 16% (95% CI; 13.6%-18.7%) | 1.12% |
| Zhao et al., 2014[23] | 1.3% (n=460) | 16.2% (95% CI; 13.7%-19%) | 1.84% |
| Walker et al., 2014[38] | 1.75% (n= 21,151) | 16.6% (95% CI; 14.3%- 19.1%) | 2.71% |

Sensitivity analysis was conducted to determine the robustness of pooled estimate. The studies selected for sensitivity analysis according to the highest[37,40], lowest[23,31,3842] prevalence rate of antidepressants containing study which resulted various pooled estimates with different weights. Among these studies Chaturvedi and colleagues[37] and Walker and colleagues[38] significantly influenced the pooled estimate of the meta-analysis.

**Supplementary Table 2.2: Alternate grouping of studies by decade**

| Decade | Number of study | Pooled estimate after sub-group analysis | Heterogeneity (%) |
|---|---|---|---|
| 1976-1985 | 3 | 0.028(0.013-0.058) | 97.29 |
| 1986-1995 | 2 | 0.259(0.123-0.466) | 98.44 |
| 1996-2005 | 5 | 0.210(0.134-0.314) | 94.32 |
| 2006-2015 | 28 | 0.159(0.131-0.191) | 99.75 |

**Supplementary Table 2.3: Quality assessment and bias risk scale**

| **Quality Assessment Scale** | **Bias Risk Scale** |
|---|---|
| 1=Low quality<br>2= Low-to-medium quality<br>3= Medium-to-high quality<br>4= High quality | 0= No risk<br>1= Low bias risk<br>2= Low-to-medium bias risk<br>3= Medium-to-high bias risk<br>4= High bias risk |

**Supplementary Table 2.4: Trends of prescription of antidepressants over time**

| Year[1] | Prescription of Antidepressants[2] | Reference No |
|---|---|---|
| 1979 | TCA-Amitriptyline, Imipramine | 31 |
| 1981-1982 | Amitriptyline, Imipramine | 32 |
| 1985 | Doxepine, Amoxapine, Amitriptyline, Imipramine | 41 |
| 1987 | Amitriptyline, Desipramine, Maprotiline | 39 |
| 1993-2005 | *SSRI, SNRI*<br>*Paroxetine, Sertraline, Citalopram, Venlafaxine, Fluoxetine, Fluvoxamine* | 52 |
| 1994 | *Dothiepin(25-225mg), Mianserin(10-30mg), Amitriptyline(50-175mg), Clomipramine(50-150mg), Other* | 37 |
| 1994-2006 | *Amitriptyline, Paroxetine, Venlafaxine, Citalopram, Mirtazapine, Others* | 48 |
| 1995 | *SSRI, TCA, MAO*<br>Dothiepin-25mg/day, Fluoxetine, Paroxetine, Sertraline, Flupenthixol, Phenelzine | 33 |
| 1997 | SSRI- Nefazodone & other | 30 |
| 2000-2005 | MAO, SSRI, SNRI, TCA | 40 |
| 2001-2004 | *SSRI, TCA, Serotonin modulators, MAOI, Other* | 49 |
| 2002 | *Paroxetine, Amitriptyline, Fluoxetine, Citalopram, Trazodone* | 28 |
| 2003-2004 | *Mirtazapine(15mg), Citalopram (10mg), Escitalopram (5mg), Fluvoxamine, Paroxetine* | 62 |
| 2005-2006 | *TCA, SSRI, TeCA, MAOI, SNRIs, Other*<br>Citalopram, Escitalopram, Mianserin, Mirtazapine | 47 |
| 2005-2009 | *SSRI, TCA, Other* | 56 |
| 2005-2010 | TCA, Other | 43 |
| 2005-2011 | SSRI, SNRI, TCA, MAO | 44 |
| 2006 | *Mirtazapine, Citalopram, Paroxetine, Venlafaxine, Amitriptyline, Fluoxetine, Duloxetine, Others* | 28 |
| 2006-2008 | SSRI/SNRIs,TCA | 49 |
| 2007 | *SSRI, TCA, Venlafaxine,* | 58 |
| 2007-2009 | *SSRI, NSSA* | 61 |
| 2008-2011 | Amitriptyline, Citalopram, Clomipramine, Dosulepin, Doxepin, Duloxetine, Escitalopram, Fluoxetine, Flupentixol, Fluvoxamine, Imipramine, Lofepramine, Mirtazapine, Nortriptyline, Paroxetine, Phenelzine, Reboxetine, Sertraline,<br>Trazodone, Trimipramine, Venlafaxine. | 38 |
| 2009 | *Mirtazapine, Escitalopram, Citalopram, Paroxetine, Amitriptyline, Trazodone, Duloxetine, Venlafaxine, Fluoxetine, Others* | 28 |

[1]Year indicated timeline present in the study or year of publication. [2]Prescription of antidepressants in italic font indicated the highest to lowest number of antidepressant user in the article.

**Supplementary Table 2.5: Alternate grouping of studies by study period**

| Decade* | Reference number | Pooled estimate after sub-group analysis | Heterogeneity (%) |
|---|---|---|---|
| 1971-1980 | 31 | 0.005(0.001-0.018) | |
| 1981-1990 | 32, 39 | 0.062(0.027-0.134) | 88.4 |
| 1991-2000 | 29, 30, 33, 35, 37, 41, 48, 52, | 0.222(0.159-0.299) | 98.88 |
| 2001-2010 | 21, 22, 28, 34, 36, 38, 40, 42, 43, 44, 45, 47, 49-51, 53-62 | 0.167(0.138-0.200) | 99.69 |
| >2011 | 23, 46 | 0.076(0.033-0.163) | 97.98 |

*Decade indicated study period present in the study or year of publication.

**Supplementary Table 2.6: Type and dose of antidepressants prescription to cancer and non-cancer patients in the hospital**

| | Cancer | | | Non-cancer | | |
|---|---|---|---|---|---|---|
| | **Depressive patient (n= 50)** | **Other mental health problem (n= 8)** | **No information of mental health problem (n= 17)** | **Depressive patient (n= 59)** | **Other mental health problem (n= 11)** | **No information of mental health problem (n= 5)** |
| Antidepressant prescription (n) | 59 | 10 | 21 | 75 | 13 | 7 |
| **Type & dose of antidepressant[1]** | | | | | | |
| Amitriptyline | | | | | | |
| <75mg | 2 | - | 3 | 3 | 1 | 2 |
| *75mg* | - | - | - | *1* | - | - |
| Citalopram | | | | | | |
| <20mg | - | - | - | 2 | 1 | - |
| *20mg* | *2* | - | *1* | *2* | - | - |
| >20mg | 1 | - | - | - | - | - |
| Desvenlafaxine | | | | | | |
| *50mg* | *2* | - | *2* | *6* | *1* | - |
| >50mg | 1 | - | - | 9 | 1 | - |
| Dothiepin | | | | | | |
| *75mg* | *1* | *1* | - | *1* | - | - |
| Doxepine | | | | | | |
| <100mg | - | 2 | - | 1 | - | - |
| Duloxetine | | | | | | |
| <60mg | 2 | - | - | 2 | - | - |
| *60mg* | *5* | - | *2* | *5* | *1* | *1* |
| >60mg | 2 | - | - | - | - | - |
| Escitalopram | | | | | | |
| *10mg* | *4* | *1* | - | *2* | *1* | - |
| >10mg | 4 | - | - | 6 | - | 1 |
| Fluoxetine | | | | | | |
| *20mg* | *4* | - | *1* | *2* | - | - |
| >20mg | - | - | 2 | 4 | 1 | - |
| Fluvoxamine | | | | | | |
| <100mg | 1 | - | - | - | - | - |
| *100mg* | *1* | - | *1* | - | - | - |
| >100mg | 1 | - | - | 2 | - | - |
| Meclobemide | | | | | | |
| <300mg | 1 | - | - | - | - | - |
| >300mg | 1 | - | - | - | - | - |
| Mirtazapine | | | | | | |
| <30mg | 5 | 2 | 2 | - | - | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *30mg* | *3* | *3* | *3* | *7* | - | *1* |
| >30mg | 3 | - | 1 | 4 | 1 | 1 |
| Nortriptyline | | | | | | |
| <30mg | - | - | - | 1 | - | - |
| *30mg* | - | - | - | *1* | - | - |
| Paroxetine | | | | | | |
| *20mg* | *2* | *1* | - | *2* | *1* | - |
| >20mg | | - | - | 2 | 1 | - |
| Sertraline | | | | | | |
| >20mg | 4 | - | 1 | 6 | - | - |
| Venlafaxine | | | | | | |
| <100mg | 2 | - | 2 | 3 | 1 | - |
| >100mg | 5 | - | - | 1 | 2 | - |

[1]indicated type and dose of antidepressants according to Anatomical Therapeutic Chemical (ATC) Classification System. Italicized entries indicated the recommended dose.

# Appendix B: PHQ-2 Screen

Mood: Over the past 2 weeks, how often have you been bothered by the following problems?

| | |
|---|---|
| Little interest or pleasure in doing things?<br>Not at all= 0, Several days= 1, More than half of the days 2, Nearly everyday= 3 | |
| Feeling down, depressed or hopeless<br>Not at all= 0, Several days= 1, More than half of the days 2, Nearly everyday= 3 | |
| Total score | |

# Appendix C: RBWH HREC Approval Letter

Queensland Government

**Metro North**
Hospital and Health Service

**Royal Brisbane & Women's Hospital**
**Human Research Ethics Committee**

Enquiries to: Alison Bowers A/Coordinator
Telephone: 07 3646 5490
Facsimile: 07 3646 5849
File Ref: HREC/15/QRBW/137
Email: RBWH-Ethics@health.qld.gov.au

Mrs Saira Sanjida
Queensland University of Technology
School of Public Health and Social Work
O Block WING A - LEVEL 1 A113-A115
Victoria Park Rd
Kelvin Grove Q 4059

Dear Mrs Sanjida,

**Re: Ref N$^{o}$: HREC/15/QRBW/137: A retrospective case-control study on the prescribing practices of antidepressants administered to cancer patients in Australia**

Thank you for submitting the above research project for single ethical review. This project was received by the Royal Brisbane & Women's Hospital Human Research Ethics Committee (RBWH HREC) **(EC00172)** on 01 April 2015 and was considered by a sub-Committee of the HREC.

I am pleased to advise that the sub-Committee has approved of this low risk project which was ratified by the RBWH Human Research Ethics Committee at its 11 May 2015 meeting.

***The waiver of consent and breach of the Australian Privacy Principles were considered justified in accordance with National Statement 2.3.10 and are approved.***

***For information on submitting a Public Health Act (PHA) application for the release of confidential health information for research purposes, please visit the Health and Medical Research website at:***
***http://www.health.qld.gov.au/ohmr/html/regu/aces_conf_hth_info.asp***

The nominated participating site for this project is:

- Royal Brisbane and Women's Hospital, Qld

**This letter constitutes ethical approval only**. This project cannot proceed until separate research governance authorisation has been obtained from the CEO or Delegate of the Royal Brisbane & Women's Hospital under whose auspices the research will be conducted.

The approved documents include:

| *Document* | *Version* | *Date* |
|---|---|---|
| Low or Negligible Risk Research Application (Submission Code: AU/10/59FD18) | LNR QLD 1.0 (2011) | 30 March 2015 |
| Covering Letter | | 01 April 2015 |
| Protocol | 2 | 28 April 2015 |
| Medicine Audit Form Data Collection Tool | 1 | |
| Clinical Audit Form Data Collection Tool | 1 | |
| Letter of Support from Senior Pharmacist RBWH | | 04 March 2015 |
| Response to Request for Further Information | | 28 April 2015 |
| Response to Request for Further Information | | 30 April 2015 |
| Curriculum Vitae of Saira Sanjida | 1 | |

Approval of this project from the RBWH HREC is valid from **06.05.2015** to **06.05.2018** subject to the following conditions being met:

- The Coordinating Principal Investigator will immediately report anything that might warrant review of ethical approval of the project.
- The Coordinating Principal Investigator will notify the RBWH HREC of any event that requires a modification to the protocol or other project documents and submit any required amendments in accordance with the instructions provided by the HREC. These instructions can be found at http://www.health.qld.gov.au/rbwh/research/hrec.asp.
- The Coordinating Principal Investigator will submit any necessary reports related to the safety of research participants in accordance with the RBWH HREC policy and procedures. These instructions can be found at http://www.health.qld.gov.au/rbwh/research/hrec.asp.
- In accordance with Section 3.3.22 (b) of the National Statement the Coordinating Principal Investigator will report to the RBWH HREC annually in the specified format, the first report being due on **06.05.2016** and a final report is to be submitted on completion of the study. These instructions can be found at http://www.health.qld.gov.au/ohmr/html/regu/reporting_templates.asp.

- The Coordinating Principal Investigator will notify the RBWH HREC if the project is discontinued before the expected completion date, with reasons provided.
- The Coordinating Principal Investigator will notify the RBWH HREC of any plan to extend the duration of the project past the approval period listed above and will submit any associated required documentation. Instructions for obtaining an extension of approval can be found at http://www.health.qld.gov.au/rbwh/research/hrec.asp.
- The Coordinating Principal Investigator will notify the RBWH HREC of his or her inability to continue as Coordinating Principal Investigator including the name of and contact information for a replacement.
- A copy of this ethical approval letter together with completed Site Specific Assessment (SSA) and any other requirements must be submitted by the Coordinating Principal Investigator to the Research Governance Office at the Royal Brisbane & Women's Hospital in a timely manner to enable the institution to authorise the commencement of the project at its site.
- Should you have any queries about the RBWH HREC's consideration of your project please contact the HREC Coordinator on 07 3646 5490. The RBWH HREC's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from http://www.health.qld.gov.au/rbwh/research/hrec.asp.

The RBWH HREC wishes you every success in your research.

Yours sincerely,

Dr Conor Brophy
**Chairperson RBWH** Human Research Ethics Committee
Metro North Hospital and Health Service
15.05.2015

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*. The processes used by this HREC to review research proposals have been certified by the National Health and Medical Research Council.

# Appendix D: QUT HREC Application Approval Letter



## Ethics application - approved - 1500000417

QUT Research Ethics Unit

Mon 1/06/2015 2:25 PM

Inbox

To: Monika Janda <m.janda@qut.edu.au>; Tracey Di Sipio <t.disipio@qut.edu.au>; Saira Sanjida <saira.sanjida@hdr.qut.edu.au>;

Cc: Janette Lamb <jd.lamb@qut.edu.au>;

1 attachment (44 KB)

UHRECSTANDARDCONDITIONSOFAPPROVAL-HUMANRESEARCH.DOC;

Dear A/Prof Monika Janda and Mrs Saira Sanjida

Project Title: A retrospective case-control study on the prescribing practices of antidepressants administered to cancer patients in Australia

Ethics category: Human - Administrative Review
QUT approval number: 1500000417 (As per Royal Brisbane & Women's Hospital Human Research Ethics Committee, Medical Services Administration, RBWH, Metro North Hospital and Health Service., Approval number: Ref No HREC/15/QRBW/137)
QUT clearance until: 6/05/2018

We are pleased to advise that your application has been reviewed and administratively approved by the Chair, University Human Research Ethics Committee (UHREC) based on the approval gained from the responsible HREC. We note this HREC has awarded the project ethical clearance until 6/05/2018.

CONDITIONS OF APPROVAL
Please ensure you and all other team members read through and understand all UHREC conditions of approval prior to commencing any data collection:
- Standard: Please see attached or http://www.orsi.qut.edu.au/human/stdconditions.jsp
- Specific: None apply

Administrative review decisions are subject to ratification at the next available UHREC meeting. You will only be contacted again in relation to this matter if UHREC raises additional questions or concerns.

Projects approved through an external organisation may be subject to that organisation's review arrangements. Researchers must immediately notify the QUT Research Ethics Unit if their project is selected for investigation / review by an external organisation.

VARIATIONS
All variations must first be approved by the responsible HREC before submission to QUT for ratification. Once approval has been obtained please submit this to QUT using our online variation form:

http://www.orei.qut.edu.au/human/var/

MONITORING

Please ensure you also provide QUT with a copy of each adverse event report and progress report submitted to the responsible HREC.

Please don't hesitate to contact us if you have any queries.

We wish you all the best with your research.

Kind regards

Janette Lamb on behalf of Chair UHREC
Office of Research Ethics & Integrity
Level 4 | 88 Musk Avenue | Kelvin Grove
p: +61 7 3138 5123
e: ethicscontact@qut.edu.au
w: http://www.orei.qut.edu.au

# Appendix E: Public Health Act- Application Approval Letter

Queensland Government

Department of Health

Enquiries to: Claudine Wilson
Health and Medical Research
Preventive Health Unit
Telephone: (07) 3328 9832
Ref QCHO/009321/RD005678

Mrs Saira Sanjida
Queensland University of Technology
School of Public Health and Social Work
O Block Wing A – Level 1 A113-A115
Victoria Park Road
KELVIN GROVE QLD 4059

Dear Mrs Sanjida

**Research Title:** **A retrospective case-control study on the prescribing practices of antidepressants administered to cancer patients in Australia**

**HREC/Project Number:** **HREC/15/QRBW/137**

I am writing to inform you that your request for access to confidential health information for the above project has been approved under the delegation of the Director-General. In accordance with Section 284 of the *Public Health Act 2005* the researchers listed in your application, received 6 May 2015 can access and use the specified confidential information, providing they act within the limits detailed in your submission.

**This approval (RD005678) commences on the date of this letter and is valid to 6 May 2018.**

**This approval relates to data for the period from 1 May 2013 to 31 December 2015 from the following repositories at the Royal Brisbane and Women's Hospital:**

- **iPharmacy**
- **Enterprise Liaison Medication System (ELMS)**
- **ieMR**

This approval means that you must undertake the responsibilities and obligations of confidentiality of the information under the provisions of the *Public Health Act 2005*. You must take all reasonable steps necessary to ensure that the confidential information is kept confidential, including storing or disposing of all data, information, documents and associated correspondence in a secure manner. Unauthorised use or disclosure of confidential information may incur a penalty under the laws of the Queensland Government. These obligations include providing notification of any change in the names of persons who will be given the information for the research.


Office
Department of Health
Level 1
15 Butterfield Street
Herston QLD 4006

Postal
HMR – Level 1
PO Box 2368
Fortitude Valley BC QLD 4006

Phone
61 7 3328 9088

Fax
61 7 3328 9115

When conducting research within the Queensland public health system, a copy of this Approval Letter must be provided to the relevant Research Governance Officer as part of your research governance application.

Please note: This letter constitutes *Public Health Act 2005* approval only. The project cannot proceed until separate Research Governance authorisation has been obtained from the relevant authority.

Please display this letter and a copy of your application when requesting the confidential information from the relevant data custodian.

You are required to provide an annual progress report and a final report at the completion of your project, to Health and Medical Research, Preventive Health Unit. Templates can be found on the web page http://www.health.qld.gov.au/ohmr/html/regu/aces_conf_hth_info.asp

Should you wish to extend your research project beyond this time or amend the study protocol, you will need to seek approval of these amendments from the approving HREC and re-apply for approval of the release of confidential data. This includes disclosing this information to and recruiting additional people to this project. Please provide a copy of your HREC approval of the amendments when re-applying.

Please feel free to contact Health and Medical Research, Preventive Health Unit on email PHA@health.qld.gov.au or phone 07 3328 9824 if you have any queries on this matter.

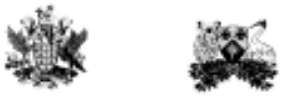
Yours sincerely

Sue Hooper

**Sue Hooper PhD**
Director, Health and Medical Research
Preventive Health Unit
Chief Health Officer Branch
Health Services and Clinical Innovation Division

11 / 5 /2015

# Appendix F: Research Governance Office Application Approval Letter



Royal Brisbane and Women's Hospital
Metro North Hospital and Health Service

Enquiries to: Professor Lawrie Powell Director of Research
MNHHS-RBWH CACR
Phone: 07 3646 2352

Mrs Saira Sanjida
Queensland University of Technology
School of Public Health and Social Work
Kelvin Grove Q 4059

Dear Mrs Sanjida,

**Re: HREC/15/QRBW/137: A retrospective case-control study on the prescribing practices of antidepressants administered to cancer patients in Australia**

Thank you for submitting your research protocol approved by Royal Brisbane & Women's Hospital Human Research Ethics Committee (RBWH HREC) on the 06.05.2015. I am pleased to inform you that authorisation has been granted for this study to be conducted at the MNHHS-Royal Brisbane and Women's Hospital. Your trial meets the principles and practices set out in the Australian Code for the Responsible Conduct of Research (2007 Universities Australia, updated 2014) and the ICH Harmonised Tripartite Good Clinical Practice (GCP) Guidelines.

The following documents approved by above mentioned HREC are specifically accepted for the MNHHS-RBWH site:

| *Document* | *Version* | *Date* |
|---|---|---|
| RBWH HREC approval letter | | 6 May 2015 |
| PHA approval letter is valid to 6 May 2018 and for data form 1 Amy 2013 to 31 Dec 2015 from RBWH: iPharmacy, Enterprise Liaison Medication System (ELMS) ieMR | | 14 May 2015 |
| Protocol | 2 | 28 April 2015 |
| Medicine Audit Form Data Collection Tool | 1 | |
| Clinical Audit Form Data Collection Tool | 1 | |
| Letter of Support from Senior Pharmacist RBWH | | 04 March 2015 |
| Curriculum Vitae of Saira Sanjida | 1 | |

When submitting electronically an HREC approved amendment to the RGO please email to RBWH-RGO@health.qld.gov.au and provide the description and the rationale for it and attach the related documents that have been approved. This will assist in the governance review to see if any further documentation is required for our MNHHS-RBWH site.

If you have any questions relating to this authorisation please contact the Research Governance Officer on 3646 8579.

I wish you continued success with your research.

Yours sincerely

Professor Lawrie Powell AC MD PhD
Director of Research, MNHHS-RBWH, Centre for the Advancement of Clinical Research
27/5/15



**Office** Royal Brisbane and Women's Hospital Butterfield Street Herston
**Postal** Post Office Herston 4029
**Phone** (07) 3646 8111
**Fax** (07) 3646 4240

# Appendix G: Data Collection Form

**Clinical Audit Form**

**Study: Prescription practices of antidepressants to patients**

Study ID:

Date: ____/____/2015

Hospital: RBWH

Other Hospital:

1. Age:

2. Sex:

- Male
- Female

3. Patient type:

- Cancer
- Non-Cancer

4. Patient status:

- Alive
- Deceased_____

5. Country of origin:

6. Living status:

7. Religion:

- No
- Does not wish to be visited

8. Insurance:

- Yes-
- No

9. Alcohol status:

- Current-
- Ex-alcoholic -
- Never -

10. Smoking status:

- Current-
- Ex-smoker-
- Never-

11. Marital status:

- Married
- Divorced/ Separated
- Never married

12. Employment:

- Yes
  - _____
- No

13. Concession status:

14. Other:

15. i. Cancer Related Information

- Date of diagnosis-
- Type-
- Stage-
- Type of Treatment-
    - Chemotherapy
    - Radio-Therapy
    - Both

15. ii. Cancer Related Information

- Date of diagnosis-
- Type-
- Stage-
- Type of Treatment-
    - Chemotherapy
    - Radio-Therapy
    - Both

16. History of depression:

i. Personal history of depression-

- Yes,
    - _____
- No

ii. Family history of depression-

- Yes,
    - _____
- No

17. Depression related information:

- Date of diagnosis
- Symptoms-
- Referral for counselling/ psychotherapy-
    - Yes
    - No
    - Who suggested? _____
- Who prescribed antidepressants?-
- Time/Date to start taking antidepressant-
- Not reported

18. Comorbidities/Pre-medical disease:

i.

ii.

iii.

iv.

v.

vi.

19. Other psychological problem-

- Yes,
  - Specify _____
- No
- Not recorded

20. Pain risk assessment: Range from 0-10

- Yes
  - Score_____
- No
- Not recorded

21. Mood risk assessment test: PHQ-2

- Yes,
  - Score_____
- No
- Not recorded

22. Further mental health assessment test-

- Yes,
  - Score_____
- No
- Not recorded

23. Allergic reaction-

- Yes_____
- No known allergy
- Not recorded

24. Adverse drug reaction-

- Yes_____
- No
- Not recorded

Notes/ Others:

**Medication Audit Form**

| No | Date | Generic/ Brand name, dose, dosage form, Rout of administration | Indication | Regular (R)/ PRN | Quantity | Comments |
|---|---|---|---|---|---|---|
| 1. | | | | | | |
| 2. | | | | | | |
| 3. | | | | | | |
| 4. | | | | | | |
| 5. | | | | | | |
| 6. | | | | | | |
| 7. | | | | | | |

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| 8. | | | | | | |
| 9. | | | | | | |
| 10. | | | | | | |
| 11. | | | | | | |
| 12. | | | | | | |
| 13. | | | | | | |
| 14. | | | | | | |
| 15. | | | | | | |
| 16. | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 17. | | | | | | |
| 18. | | | | | | |
| 19. | | | | | | |
| 20. | | | | | | |
| 21. | | | | | | |
| 22. | | | | | | |
| 23. | | | | | | |
| 24. | | | | | | |

Ceased Medication

| No | Date | Generic/ Brand name, dose, dosage form, Rout of administration | Reason | Comments |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |
| 3. | | | | |
| 4. | | | | |
| 5. | | | | |
| 6. | | | | |

Note/ Others: